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Urinary excretion of cytomegaloviruses by children with generalized neoplastic disease

Correlation with clinical and histopathologic observations

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THE patient with lymphoreticular malignancy or leukemia, particularly while under intensive corticosteroid therapy and chemotherapy, might be expected to (a) develop activity of viruses previously latent, or (b) present an unusual response to agents newly acquired. Indeed, unusual patterns of disease in patients with malignancy and also infected with certain intranuclear inclusion-producing viruses have been reported; varicella-zoster virus and the agents responsible for cytomegalic inclusion disease particularly have been incriminated. For example, of the 15 cases of disseminated cytomegalic inclusion disease (CID) in adults cited by Symmers,[1] 10 occurred in patients who also had leukemia, Hodgkin's disease, or lymphosarcoma.

As tissue culture techniques are available for the isolation of the etiological agents of cytomegalic inclusion disease[2, 3] and since viruria has been noted frequently in patients with CID,[4, 5] it seemed of interest to investigate the occurrence of viruria in children

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with malignant diseases. It was further desired to obtain information bearing on host-parasite relationships in such a circumstance through attempts to correlate the pattern of viruria with pertinent serologic, clinical, and histopathologic data. CID has been considered to be the result of generalized infection with a single type of virus, often termed salivary gland virus (SGV), an agent apparently widely disseminated in latent form.[6] However, recent work suggests that the CID-SGV viruses are not antigenically homogeneous but instead should be considered as a group of related agents; for this group, the term "cytomegalovirus" has been proposed.[7]

This report describes the detection and the pattern of urinary excretion of a cytomegalovirus in 4 of a group of 50 patients with malignant disease, as well as the concurrent isolation from the urine of one of these patients of an adenovirus. The isolation of an inclusion-producing virus from the spleen of a fifth child is noted in the absence of viruria.

MATERIALS AND METHODS

Tissue cultures. Primary explant cultures derived from human embryonic skin-muscle or postnatal foreskin were used to detect cytomegaloviruses in investigation of the group of 50 children. Monolayer cultures of trypsinized human amnion were also employed in the testing of urine specimens from 34 patients in an effort to isolate additional agents. The nutrient fluid consisted of bovine amniotic fluid (45 per cent), Hanks' balanced salt solution (45 per cent), inactivated horse serum (5 per cent), and beef embryo extract (5 per cent); antibiotics, soybean trypsin-inhibitor, and phenol red were added. Nutrient fluids were changed at 3 to 5 day intervals. Inoculated cultures were incubated in rotating racks at 35° C. and were examined twice weekly for a period of 30 days.

Tentative identification of the cytomegalovirus strains was based on the observed morphologic and cultural characteristics which were in accord with those previously described.[2, 3] It is to be noted that serologic identification of newly isolated strains is not now feasible; adaptation achievable by repeated subculture is a necessary prerequisite. For serial cultivation, infected tissues were scraped, ground with alundum in nutrient fluid, and 0.2 ml. aliquots of the resulting uncentrifuged supernatant fluid were used as inocula. For histologic studies fixation was with Bouin's solution, the cell outgrowth was imbedded by the collodion technique,[8] and preparations were stained with hematoxylin and eosin.

Serologic tests. All sera were inactivated at 56° C. for 30 minutes. For screening neutralization tests, inactivated sera were diluted 1:4 and incubated at 5° C. for one hour with equal parts of tissue culture adapted cytomegalovirus of known titer diluted so that the final mixture contained approximately 100 ID_{50} per 0.2 ml.; two strains obtained from CID patients (Davis, Kerr[3, 5]) and the AD 169 strain supplied by Dr. W. P. Rowe[9] were employed. Neutralization tests were observed for a period of 30 days. Serologic techniques employed in the study of the adenovirus isolate are described below.

Collection and testing of urine specimens. Urine specimens were kept at 5° C. until processed and inoculated into tissue culture, usually within 2 hours of voiding. Following centrifugation at 2500 r.p.m. for 30 minutes, 0.2 ml. of the supernatant was inoculated into each of two human fibroblastic tissue cultures and frequently also into two human amnion cultures. Similarily, 0.1 ml. samples of urine sediment were inoculated into one tube of each tissue type. An uninoculated control tube for each of the two cell types was maintained in parallel. Each urine cultured was also examined for the presence of intranuclear inclusion bearing cells as follows. The remaining sediment was streaked on clean glass slides covered with a thin film of 25 per cent crystalline bovine albumin in normal saline solution; the preparation was fixed while still moist in equal parts of absolute ethyl alcohol and ethyl ether (U.S.P.) for a period of 10 minutes. Fixed preparations were placed in

2 per cent Giemsa in Sorenson's phosphate buffer (pH 7.1) for a period of 40 minutes. Within limits of patient availability attempts were made to collect multiple urine specimens with particular emphasis placed on those known to have viruria.

Clinical material. Fifty children, ranging in age from 5 months to 15 years, with a median age of 6 years, 8 months, were selected at random from patients undergoing treatment at the Children's Cancer Research Foundation, Boston. Thirty-five were males. The diagnoses in this group were as follows: acute leukemia 43, Hodgkin's disease 3, lymphosarcoma 3, and malignant lymphoma 1. All but 6 patients were being treated with one or more drugs and all had received a blood transfusion at the time the first urine specimen was collected. Antimetabolite therapy was being administered to 27 children; 17 were receiving 4 amino-N^{10} methylpteroylglutamic acid (Methotrexate) and 10 patients 6-mercaptopurine. Corticosteroid suppressive therapy was being administered to 21 patients at the time the initial urine specimens were inoculated. Three children were receiving Vincaleukoblastine.* Cultures were obtained at varying intervals following the establishment of the primary diagnosis.

RESULTS

A. Recovery of cytomegalovirus from urine. Ninety-eight urine specimens were cultured; 27 of the patients were examined once and the remainder two or more times. Four male patients yielded strains of cytomegalovirus, and from these patients 12 separate isolations were made. The pattern of virus excretion as related to the duration of the primary illness is summarized in Table I. When virus was isolated, focal lesions in the fibroblastic outgrowth of the cultures were noted first between the seventh and twenty-fourth days following inoculation. With strains from 3 patients the expected progression of the cytopathic process occurred and generalized involvement of the tissue developed between the forty-fifth and the one hundred twentieth days, at which time the agents were subcultured. Strains recovered on three different occasions within an 8 day period from the urine of the fourth patient showed regression of the cytopathic process about the twenty-first day after inoculation and the disappearance of lesions around the thirtieth day; this regression was possibly due to the presence of suboptimal conditions for tissue growth. The three strains that progressed to generalized involvement of fibroblastic tissue induced intranuclear inclusions demonstrable on staining with hematoxylin and eosin.

Although, in general, cells of epithelial origin appear less sensitive than fibroblastic cells as indicators of the presence of the cytomegaloviruses, one of the 66 urine specimens tested in fibroblastic cells and in amnion cells was positive in both types of culture. In this instance the fibroblastic cultures developed focal lesions on the seventh day while the amnion cultures first showed changes on the twenty-third day. The cytopathic effects in amnion were characterized by swollen, rounded cells that contained intranuclear inclusions demonstrable with a magnification of 100× in unstained cultures and that occurred singly or in small groups. Passage of this material to new cultures of amnion produced cytopathic changes by the twelfth day.

B. Occurrence of mixed viruria. One patient demonstrated to have cytomegalovirus viruria was also excreting a second agent. The isolations from this individual (R. O.), a 9-year-old boy with acute leukemia, are summarized in Table II. Two agents, a cytomegalovirus and a second, tentatively identified as an adenovirus Type 7, were recovered on three occasions under circumstances suggesting that concurrent viruria occurred over a period of 46 days.

The random distribution of the two agents in positive cultures permitted selection of one free of cytomegalovirus but possessing changes that were compatible with adenovirus cytopathogenicity. Also subculture from cultures of fibroblastic cells showing a mixed cytopathic process to human amnion

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Table I. Pattern of cytomegalovirus excretion in four patients

Patient	*Age*	*Diagnosis*	*Time in weeks from date diagnosis of malignancy made* 0 . . . . 5 . . . . 10 . . . . 15 . . . . 20 . . . . 25 . . . . 30 . .
R. S.	2	Hodgkin's disease	+ ++ D
R. O.	9	Leukemia	+ + + + - - D
D. D.	7	Leukemia	+ + + D
J. M.	4	Leukemia	+ - - - + + L

+ = Cytomegalovirus isolated from urine.
- = Urine negative for virus.
D = Dead.
L = Living.

cultures resulted in the rapid overgrowth and segregation of the adenovirus component. The second agent was subcultured to HeLa and human amnion cells and pools of virus made. A complement fixing antigen was prepared from third passage material in HeLa cells. With this antigen, specific fixation occurred in the presence of a 1:64 dilution of convalescent phase human sera obtained from a known adenovirus infection; negative reactions were obtained with the respective acute phase serum, as well as with a control antigen. Therefore, neutralization tests with 100 ID_{50} of the unknown virus and appropriate dilutions of adenovirus type specific rabbit serum (Types 1 through 8) were performed in human amnion cultures; significant neutralization occurred only in the presence of Type 7 antiserum.

C. Correlative clinical, histopathologic, and serologic data on the patients excreting cytomegalovirus.

Examination of the urine sediment. Intranuclear inclusions were readily demonstrated in the urine sediments of one patient (R. S.). Of the eight urine specimens known to contain virus that were obtained from the remaining 3 patients, only in three could inclusions be found in the stained sediments, and in each instance these were very few in number. Urine sediments from 45 patients apparently not excreting virus were also examined; only in one were suggestive intranuclear bodies observed. This patient, at necropsy, had no morphologic evidence of viral infection of the urinary tract.

Correlative clinical data. In only one instance was there an apparent association between the occurrence of cytomegalovirus and the clinical picture. This patient (D. D.), a 7-year-old boy, was found to have acute leukemia in February, 1959. On Aug. 24, 1959, he was admitted to the hospital with fever, and respiratory distress of 4 days' duration. Respirations were shallow and increased in rate; basilar râles and decreased breath sounds were heard on auscultation. Roentgenograms of the chest taken on the day of admission showed extensive pulmonary infiltration in both lower lobes. Bacteriologic cultures of the nose, throat, and blood failed to demonstrate a bacterial pathogen. Although antibiotic therapy was followed by clinical and roentgenologic improvement, the patient continued to have recurrent episodes of fever, an increased respiratory rate, and râles in the chest. During the 8 week period prior to his death on Oct. 18, 1959, cytomegalovirus was isolated from the urine on Sept. 1 and on Sept. 15, 1959. An autopsy was performed at the Stanford University School of Medicine.

Table II. Patient R. O. Virus isolations from urine during 5 month period prior to death on May 13, 1959

	Cytomegalovirus	*Adenovirus Type 7*
December	+	+
January	+	+
February	+	+
March	ND	ND
April	+	0
May	0	0

+ = Urine positive for virus.
0 = Urine negative for virus.
ND = Not done.

Through the courtesy of Dr. William P. Creger a summary of the postmortem findings and fixed lung tissue were obtained. Of particular interest was the finding of numerous large cells containing discrete intranuclear inclusions in sections of the lung (Fig. 1). Other organs, including the kidneys, were negative for cytomegalic cells.

Although 2 patients (R. O., R. S.) were excreting cytomegalovirus one month prior to death, morphologic evidence of viral activity could not be demonstrated at autopsy. In one of these (R. O.) attempts to culture virus from the urine, blood, saliva, and cerebrospinal fluid 3 days prior to death had been unsuccessful. One patient (J. M.) was excreting virus when tested one month after the onset of symptoms, and 7 days after specific diagnosis was made and corticosteroid therapy initiated. Then three urine specimens tested during the following 5 months were negative for virus; this coincided with a period of clinical remission. Clinical exacerbation of the leukemic process occurred at the sixth month; at this time virus was again demonstrable in the urine.

Sera from the 4 excretors of virus were tested for the presence of neutralizing antibody against two strains of cytomegalovirus from CID patients (Davis, Kerr) and against one from adenoidal tissue (AD 169). Detectable neutralizing antibody for the three agents could not be demonstrated in the 4 sera tested. Serum from the patient with mixed viruria was also tested for adenovirus neutralizing antibody. The homologous adenovirus strain in a final concentration of 100 ID_{50} was mixed with inactivated serum appropriately diluted, incubated at 5° C. for one hour, and then inoculated into cultures. Complete neutralization occurred at a serum dilution of 1:128 after 28 days.

D. Other observations. The urine of a patient with leukemia was observed to produce cytopathic changes, characterized by diffuse cell rounding, within 24 hours in fibroblastic cultures. On staining, this phenomenon was found to be secondary to the apparent accumulation of mitotic figures in metaphase. Investigation revealed that the patient was

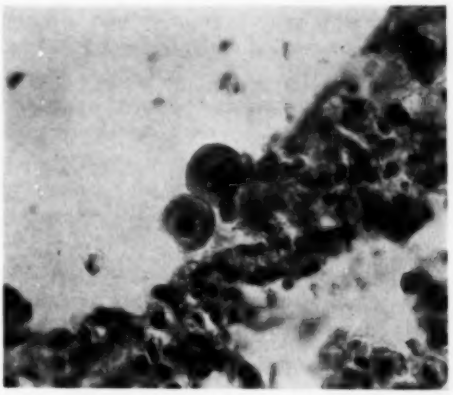

Fig. 1. Cytomegalic inclusion cells observed postmortem in the lungs of patient D. D. (Hematoxylin and eosin stain. Original magnification ×800.)

receiving Vincaleukoblastine; this material, an alkaloid derived from *Vinca rosea*, produces metaphase arrest in certain cell types in vitro.[10] On further investigation, six additional urine specimens obtained from 3 patients receiving this compound produced similar cytopathic changes. The phenomenon was demonstrable in one instance following inoculation of urine diluted 10^{-4}. The response was much less marked in amnion cells. The effect did not persist when the medication was discontinued. Further, the addition of Vincaleukoblastine in a concentration of 0.2 γ per milliliter of medium to cultures of human fibroblastic tissues reproduced the changes noted within a 24 hour period.

Intranuclear inclusion containing cells were noted in tissue obtained at splenectomy from a 4-year-old boy with Hodgkin's disease and hypersplenism on histopathologic examination by the frozen section technique. A portion of the spleen, kept at 5° C. for 48 hours, was ground and a 10 per cent suspension in nutrient fluid inoculated into human fibroblastic cultures. In 24 hours focal and diffuse cell rounding was noted with progression to a generalized cytopathic effect in a period of 6 days. Serial cultivation of the nutrient fluid from the involved cultures was found to produce cell rounding

in 24 hours. Subculture to amnion cultures produced rounding of both single cells and groups of cells 23 days after inoculation. Intranuclear inclusion bearing cells similar to those produced by the cytomegaloviruses were demonstrated on staining with hematoxylin and eosin. Four attempts to recover virus from the urine of this patient performed 10, 14, 42, and 55 days after operation were negative, as were attempts to isolate virus from the blood on the fourth day and from saliva on the forty-second day.

DISCUSSION

Only two types of virus, an adenovirus and strains of cytomegalovirus, were recovered from the urine of children with progressive neoplastic disease. Both are known to persist in the human host in the absence of overt manifestations of infection. At present, a growing list of viral agents including mumps,[11] measles,[12] herpes simplex,[13] and Coxsackie[14] viruses have been recovered in vitro from the urine of infected individuals; the failure, therefore, to recover other agents is of interest per se.

The host-parasite relationships of the cytomegaloviruses are unusual and the factors involved in the pathogenesis of cytomegalic inclusion disease not yet defined. Of 2 children with leukemia and one with Hodgkin's disease who had cytomegaloviruria and subsequently were followed to necropsy, only one showed morphologic evidence at postmortem of a specific process attributable to cytomegalovirus and this in the form of bilateral interstitial pneumonitis. There was apparent cessation of virus excretion in one leukemic child. It is not possible at present to assess the relationship, if any, between the neoplastic process, the therapy therefor, and concurrent viral infection; however, cytomegalovirus viruria may occur in a significant percentage of "normal" children in an institutional environment.[6] The failure to demonstrate specific neutralizing antibody for 3 strains of virus in sera from the 4 cytomegalovirus excretors is not necessarily significant in view of the antigenic heterogeneity of the group[7] and the fact that the tests were run, of necessity, with heterologous strains of virus. On the other hand, sera from the one child with leukemia who was also excreting an adenovirus contained significant levels of antibody for that agent.

The unusual cytopathic change induced by urines from patients under therapy with Vincaleukoblastine has been observed following introduction of the compound into cultures of a variety of cell types.[10] That the compound, or an active metabolite thereof, appears in the urine of patients under therapy is of biologic interest. Further, the changes in living cells are such that they might easily be misinterpreted as being the result of specific viral activity.

SUMMARY

To explore the role of latent viruses as possible causes of complicating infections in the terminal phases of illness due to neoplastic disease, a study was made of the occurrence of viruria, with particular reference to the cytomegaloviruses, in a group of 50 children with leukemia, lymphoma, or Hodgkin's disease. Cytomegalovirus was isolated two or more times from the urine of 3 patients with leukemia and of one with Hodgkin's disease. One of these patients had recurrent respiratory symptoms; at necropsy cytomegalic inclusion disease of the lungs was demonstrated. On the other hand, in 2 of the viral excretors followed to autopsy, no postmortem morphologic evidence of activity could be found.

Of interest was the fact that one leukemic patient over a period of several weeks concurrently excreted two viruses in the urine, an adenovirus and a cytomegalovirus.

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The response of infants and children to Asian influenza vaccine administered by intradermal and subcutaneous routes

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THE effectiveness of influenza vaccine in reducing the incidence of influenzal infection has been established.[1-4] The relative importance of the volumes of vaccine administered and of the routes of administration has not been clarified, however. Most of the earlier studies were concerned with the antibody response produced by 0.1 ml. of vaccine administered intradermally in comparison to that resulting from 1.0 ml. of vaccine administered subcutaneously.[5-10] In these instances, it was uncertain whether the extent of the antibody response was related to the volume of the vaccine or to the route of administration.

The study of McCarroll and Kilbourne[11] provides a more precise evaluation of the relative value of routes of inoculation; they compared the responses to equal volumes of vaccine administered by different routes in adults and concluded that the antibody response following subcutaneous injection was equivalent to that following intracutaneous administration. Such information has not been available in infants and young children.

The present study is concerned with the antibody response of children ranging in age from 2 months to 5 years to a single dose of 0.1 ml. of Asian influenza vaccine administered intradermally and subcutaneously, respectively.

MATERIAL AND METHODS

A total of 180 infants and children ranging in age from 2 months to 5 years were inoculated subcutaneously or intradermally with a single dose of 0.1 ml. of monovalent Asian influenza vaccine* containing 200 CCA units per milliliter. Pre- and 2 weeks postimmunization serum specimens were collected from 89 infants and children. All sera were inactivated for 30 minutes at 56°C. before being tested for antibody titer. The pre- and postimmu-

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nization sera of each individual were tested simultaneously for their antibody titer.

The hemagglutination inhibition test was performed with the use of the nineteenth egg passage of the Japan 305 strain as the test virus. This strain was used because it did not react with nonspecific serum inhibitors even at an initial dilution of 1:2, and no prior treatment of the sera was needed. The procedure for hemagglutination inhibition test was essentially that described by Boger and Liu.[8]

RESULTS

The antibody response of the 89 infants and children was not significantly different to equal volumes of vaccine administered intracutaneously or subcutaneously (Table I).

Bruyn and associates[12] found that 0.125 ml. of either PR 8 or Lee strain of influenza vaccine given subcutaneously gave a response similar to that of 0.1 ml. administered intracutaneously. Although the volumes were not identical they were close enough to suggest that there was no great difference in the antibody response to equal quantities of vaccine, whether it was administered subcutaneously or intracutaneously.

REACTIONS

Table II shows the incidence of febrile reactions to the vaccine administered by the two routes of administration. It is interesting to note that there was a higher incidence of febrile reactions in individuals who received 0.1 ml. of the vaccine intradermally than in those of the same age range who were given 0.1 ml. of the vaccine subcutaneously.

All the children who received 0.1 ml. vaccine intradermally had some local reaction consisting of a small area of erythema and induration at the site of inoculation with slight tenderness and itching for 2 to 3 days. Only 2 of the 94 children who received 0.1 ml. vaccine subcutaneously had mild local reactions consisting of pain and induration.

DISCUSSION

The data indicate that the antibody response following subcutaneous inoculation is equivalent to that resulting from intracutaneous injection, when equal volumes of influenza vaccine are given. For infants and children under 5 years of age, 0.1 ml. of the vaccine given subcutaneously is as effective as 0.1 ml. of the vaccine given intracutaneously in stimulating antibody formation.

Table I. Antibody response to a single injection of 0.1 ml. of Asian influenza vaccine administered intracutaneously and subcutaneously

	Intracutaneous route				*Subcutaneous route*			
Age of patients	*No. immunized*	*No. responded*	*% responded*	*Geometric mean titer**	*No. immunized*	*No. responded*	*% responded*	*Geometric mean titer**
2 mo. to 1 yr.	13	8	61	2.7	15	11	73	3.0
1 to 3 yr.	16	13	81	4.3	14	13	93	4.2
3 to 5 yr.	19	16	84	3.4	12	10	83	2.5

*Expressed as initial dilution of sera (final dilution after addition of virus suspension and red blood cells is 3 times the initial dilution).

The titer shown above represents primary response to vaccine in children who had no detectable titer prior to immunization.

Table II. Incidence of febrile reactions to inoculations of 0.1 ml. of influenza vaccine according to age and route of administration

	Subcutaneous route		*Intracutaneous route*	
Age group	*No. immunized*	*No. with febrile reactions*	*No. immunized*	*No. with febrile reactions*
2 mo. to 2 yr.	52	10 (19.2%)	49	17 (34.7%)
2 to 5 yr.	42	5 (11.9%)	47	13 (27.7%)

These results extend and confirm the previously published observations showing that the intradermal route is not superior to the subcutaneous route when equal volumes of vaccine are employed.[11, 12]

Antibody titers determined by the hemagglutination inhibition test have been shown to correlate closely with titers obtained by the neutralization test.[13] In our observation using the nineteenth egg passage of the Japan 305 strain of influenza virus, we have found the hemagglutination inhibition test somewhat less sensitive in detecting small amounts of antibody than the neutralization test. However, all serum samples positive by the hemagglutination-inhibition test were also positive by the neutralization test. Definite information concerning the exact level of hemagglutination inhibition antibody which would be protective against Asian influenza infection is not available. According to the results obtained on convalescent-phase sera from serologically proved cases of Asian influenza, however, Hilleman[10] stated that a geometric mean titer of 1:14.3 should be a protective antibody level against Asian influenza infection. In the present series the antibody response to a single dose of 0.1 ml. of Asian influenza vaccine administered to infants and children was of low order regardless of the route of administration. It is obvious that more than one injection of the vaccine is necessary in order to induce high antibody levels. The optimal number and volume of the doses of vaccine and the appropriate intervals of time between injections for primary immunization and for booster effects are not established.

SUMMARY

In infants and children ranging in age from 2 months to 5 years, 0.1 ml. of a vaccine containing 200 CCA units per milliliter of Asian influenza virus gave equal antibody responses when injected by either the intracutaneous or the subcutaneous route. There were fewer febrile and local reactions with an equivalent volume of vaccine given by the subcutaneous route in comparison with administration by the intracutaneous route. It appears that, for infants and children under 5 years of age, the subcutaneous route of administration should be used since it is simpler and causes fewer and less severe febrile reactions and since there is less chance for leakage of vaccine.

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Studies on 5-hydroxyindole metabolism in autistic and other mentally retarded children

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THERE is little doubt that the biogenic indolealkylamine, 5-hydroxytryptamine (5-HT, serotonin), plays some role in neuronal function in the brain, although the nature of this role is still unclear. Various theories have been developed regarding the mechanism of action of 5-HT, and of its possible relationships to mental disease,[1-3] but there has been no widespread acceptance of any of these hypotheses.[4-6]

The search for evidence of abnormal 5-hydroxyindole metabolism in schizophrenia has been vigorously pursued for the past 6 years without producing any clear-cut evidence of such an abnormality. Most investigators now agree that there is no evidence of a generalized disturbance in the metabolism of 5-HT in schizophrenia.[7-9] Recently, Pare and colleagues[10-11] have published data on blood 5-HT and urine 5-hydroxyindoleacetic acid (5-HIAA) levels in mentally defective children. They initially reported that persons with phenylketonuria have low blood 5-HT levels; they have subsequently confirmed this observation and have also provided data indicating that other defectives have abnormally *high* 5-HT levels.[12] These workers are presently attempting to make meaningful correlations between specific diagnoses and elevations of blood 5-HT.[13]

Sutton and Read[14] have reported evidence of the decreased ability of one child with infantile autism to convert tryptophan to urinary indole acids. On the other hand, Shaw and co-workers[15] have administered 3 Gm. of L-tryptophan to schizophrenic and nonschizophrenic children. They found no difference in the increase of 5-HIAA excreted by either group.

One of us had been engaged in the clinical characterization of a group of 50 children with the diagnosis of infantile autism who had been committed to the Southbury Training School.[16] Blood levels of 5-HT determined on a few of these children were considerably higher than those heretofore obtained in our laboratory from a heterogeneous group of patients (excluding those with carcinoid syndrome). On the basis of

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Table I. Comparison of blood serotonin levels in autistic and nonautistic retarded children, t-tests (mean difference)*

	Normal control	*Autistic*	*Non-autistic low-grade*	*Middle and high-grade*
Normal control	—	4.04‡	3.02†	1.00
Autistic		—	1.00	3.57†
Nonautistic low-grade			—	2.67†
Middle and high-grade				—
Mean blood 5-HT	.065	.141	.128	.072
Standard deviation	.017	.078	.045	.033
Number	4	23	7	12

*t's calculated by the Cochran-Cox method of testing the significance of the hypothesis of equality of means, weighted in terms of their respective variance.

†Significant at or beyond the 5 per cent level of confidence.

‡Significant at or beyond the 1 per cent level of confidence.

these findings and in view of the suggestive data previously mentioned, it was decided to study some aspects of 5-hydroxyindole metabolism in these children.

EXPERIMENTAL METHODS

Blood 5-hydroxytryptamine and urine 5-hydroxyindoleacetic acid were determined on 23 children whose clinical diagnosis was infantile autism. Their ages at the time of the investigation were 6 to 18 years with an average age of 10.8 years. The criteria for establishing this diagnosis and the clinical data are discussed elsewhere.[16] Briefly, these criteria can be outlined as follows:

1. Evidence of a severe personality disorder characterized by preoccupation with self and unrelatedness to people in the environment.

2. Presence of a history indicating the onset of this disorder during the first 2 years of life as manifested by the failure to develop the expected patterns of relationships to parents or other guardians.

3. Absence of a history of serious motor retardation which is associated with most forms of gross brain defect.

Other defective children roughly matched for age and sex were also studied. Multiple determinations were made on all children.

Tryptophan loads consisting of 1 Gm. of L-tryptophan daily for 3 days were given to some of the children. This amount was estimated to be approximately twice the average daily intake of L-tryptophan in the diet. Blood 5-HT was estimated before and after this procedure.

Blood samples were uniformly drawn in the early afternoon and kept frozen for periods of up to 24 hours until extractions were performed. The clotted blood was homogenized and 5-HT extracted with 20 volumes of acetone.[17] The acetone extract was dried in vacuo and kept at −18° C. prior to assay. Estimations of 5-HT were performed by bioassay on the heart of the clam *(Venus mercenaria)* or on the rat uterus in estrus. The recovery of added 5-HT from whole blood has been a difficult problem for many investigators concerned with the absolute significance of their data. Hardisty and Stacey[20] reported an average of 30 per cent recovery of 5-HT from human red blood cell suspensions with the use of 95 per cent acetone for extraction. Kärki and Paasonen[21] mention a consistent 35 to 45 per cent recovery from rat blood with 95 per cent acetone. Cargill-Thompson and associates[22] have obtained extremely variable recoveries using buffered butanol as the solvent (39 to 96 per cent; average 56 per cent). They report much better recoveries in certain animal species (cat, dog, goat, ox, and rat). Humans, along with guinea pigs, rabbits, sheep, and pigs, yielded poor recoveries. Correale[23] has stated that 80 per cent acetone gives much better recoveries of 5-HT from brain than 95 per cent acetone. Recently, evidence has been presented indicating that free 5-HT in blood is rapidly oxidized by oxyhemoglobin in vitro.[24] It has been noted that the addition of EDTA[25] or ascorbic acid[26] improves the recovery of added 5-HT from blood.

We also have found great variability in

the recovery of added 5-HT from blood (25 to 75 per cent). 2-Mercaptoethanol, a potent reducing and chelating agent, in 0.0001 to 0.01 molar concentration in blood did not improve recovery. The use of 80 per cent acetone in two experiments gave the same recovery as 95 per cent acetone. Ascorbic acid interfered with the function of the test object and could not be used. EDTA was not tested in these experiments.

In spite of these poor recovery rates based on addition of exogenous 5-HT, we have found that the levels of endogenous 5-HT measured in blood have not shown the same extreme degree of fluctuation. Twelve determinations done at different times on one normal adult gave a mean 5-HT level of 0.090 gamma per cubic centimeter with a standard deviation of 0.018. The multiple determinations on children with mean blood 5-HT values over 0.200 gamma per cubic centimeter showed consistent elevations. Waalkes,[25] using EDTA with a fluorimetric method (which always yields higher numerical values than those derived by bioassay), has reported average blood 5-HT levels of 0.130 gamma per cubic centimeter with a range of 0.090 to 0.180.

We believe 5-HT artificially added to blood is more susceptible to destruction than endogenous 5-HT. Although we do not regard our data as indicative of absolute levels of blood 5-HT (our data are probably lower), we have found our results to be more consistent than the highly variable recovery data would indicate.

Urine samples were collected in the morning, and 5-HIAA assayed according to the method of McFarlane and co-workers.[18] The ether used for extraction was washed with 2 per cent ferrous sulfate, and acidified distilled water was used throughout. Urinary creatinine was determined by use of the Jaffé reaction,[19] and results were expressed as micrograms of 5-HIAA per milligram of creatinine.

RESULTS

The patients studied can be roughly divided into three groups:

A. Mildly retarded children with intelligence quotients of 60 to 80 obtained with the revised Stanford-Binet test, e.g., familial "subcultural" defective children, high-grade Mongols.

B. Children with the diagnosis of infantile

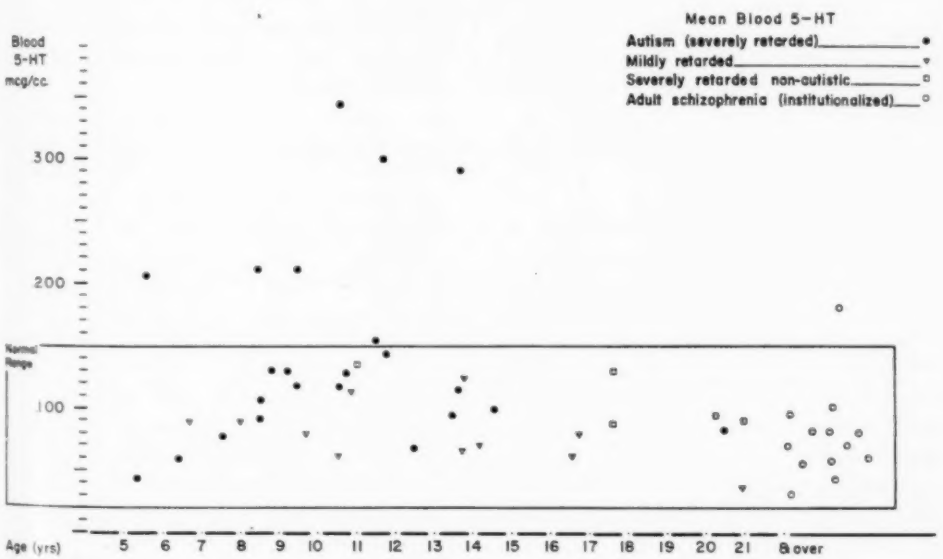

Fig. 1. Mean blood 5-HT levels for individuals of each group.

autism who function on a severely retarded level. These children are usually not trainable and are segregated with other low-grade retarded children. Features of this syndrome are described in detail in the study of Schain and Yannet.[16]

C. Severely retarded children without a diagnosis of autism (I.Q. under 20), e.g., congenital cerebral defect, diffuse encephalopathy. These children live in the same cottages as the autistic children.

The mildly retarded children (Group A) had blood 5-HT levels averaging 0.072 gamma per cubic centimeter with a range of 0.042 to 0.156, which is similar to the normal values obtained in this laboratory. The autistic children had average blood 5-HT levels of 0.141 gamma per cubic centimeter with a range of 0.033 to 0.540. When the data from this group are studied individually, it can be seen that certain of the autistic children have particularly high levels (Fig. 1). Six of the 23 autistic children had mean levels over 0.200 gamma per cubic centimeter, a figure which is well above the range of normal for our laboratory (0.02 to 0.15 gamma per cubic centimeter). One of these cases had 11 determinations ranging from 0.210 to 0.540 gamma per cubic centimeter with an average of 0.342 gamma per cubic centimeter. Values for adult chronic schizophrenic patients are within the normal range.

A small group of nonautistic low-grade defective children were also studied. Their average blood concentration of 5-HT was 0.128 gamma per cubic centimeter. This is not significantly different from the autistic group as a whole, although one of the individual values of one child was over 0.200 gamma per cubic centimeter (Table I).

Tryptophan loads were given to 4 autistic children. This was followed by no consistent change in blood 5-HT.

Some children were receiving phenobarbital, Dilantin, or chlorpromazine at the time of this study. None of these drugs seemed to be associated with any changes in blood 5-HT. Three children on reserpine had no detectable blood 5-HT. This is in accord with the well-known observation of Brodie,[1] subsequently confirmed by many investigators, that reserpine depletes most tissues of 5-HT.[27] Consequently, patients on reserpine were not included in this study.

Urine 5-HIAA values were distinctly higher in the autistic group than in the mildly retarded group when expressed as gamma per milligram of creatinine (Table II). The absolute amount of 5-HIAA per milliliter of urine was similar in both groups; creatinine values, however, were much lower in the autistic children, indicating greater dilution of urine. None of the 5-HIAA results can be considered as significantly abnormal. The 24-hour excretion of 5-HIAA probably falls in most cases within the generally accepted values of 2 to 9 milligrams.

DISCUSSION

These results confirm the impressions of Pare, Sandler, and Stacey[12] that mentally defective children have elevated levels of 5-HT in blood. Our data would indicate that the elevations tend to be present only in some of the more severely defective chil-

Table II. Comparison of urinary 5-HIAA and blood 5-HT in 12 autistic and 6 mildly retarded children

Autistic children		*Mildly retarded children*	
5-HIAA (gamma/mg. of creatinine)	*Mean blood 5-HT (gamma/ml.)*	*5-HIAA (gamma/mg. of creatinine)*	*Mean blood 5-HT (gamma/ml.)*
8.3	.148	2.2	.068
10.0	.343	1.6	.126
0.9	.079	0.8	.080
2.2	.202	2.1	.073
5.7	.125	1.8	.077
5.2	.283	1.2	—
4.5	.097		
8.6	.119		
6.6	.290		
4.4	.065		
8.4	.202		
4.8	.205		
Mean 5.9	.141	1.6	.072

dren. Consistent unusual elevations of blood 5-HT were found only in children with the diagnosis of autism, although the mean blood 5-HT level of other severely retarded children was higher than that of the mildly retarded group. Sandler[13] has apparently found high levels in various clinical groups; details of this study are not available as yet. We have analyzed the histories of the 6 autistic children with the highest blood 5-HT levels and have been unable to find any specific correlative signs. The presenting symptomatology of these 6 children did not differ from that of the other autistic children who had normal 5-HT levels. The only feature that appeared at all noteworthy was the absence of seizure disorders in any of the 6 autistic children with elevated 5-HT. The frequent occurrence of seizures in autistic children was one of the most significant results of the clinical study of these children.[16] Only 1 of the 6 children with elevated blood 5-HT had had even one questionable seizure.

It is difficult to decide at this time whether the elevation of blood 5-HT is meaningfully related to the behavioral disorders of these children. Diet and exercise are two important factors that may affect the levels of metabolites in body fluids. The lack of an effect of a 3-day tryptophan load on blood 5-HT in our studies would seem to indicate that this parameter is not immediately influenced by dietary changes. We do not know the effect of prolonged dietary variations on blood levels of 5-HT. Sandler has not been able to correlate physical activity with 5-hydroxyindole production in mentally defective spastic persons. We have not studied the factor of exercise. In general, the autistic children are much less active than those in the mildly retarded group.

It may be that as biochemical factors are more intensively studied in children presenting with mental retardation, the same kind of problem will appear that is well known in investigations of adult schizophrenia, viz., the increased variability in many biochemical and physiologic parameters in this disease. This feature has provided frequent false leads in the search for a specific metabolic defect associated with schizophrenia.[8] The reasons for this variability are not readily apparent, but its repeated occurrence has made most investigators of the biology of schizophrenia highly skeptical about the significance of changes in specific biochemical parameters. It is quite possible that the same kind of variability will be noted in mentally defective children. We do not know, as yet, if the abnormally elevated blood concentrations of 5-HT in some of these children will be an example of this phenomenon. The elevations do occur consistently within individuals, and the possibility of identifying a specific subgroup by the measurement of 5-HT remains to be explored.

Severely retarded children receiving custodial care in even the best of institutions live radically different lives as compared to their normal peers. It is difficult to assess the effect of these differences on parameters measured. It would seem worth while in investigating developmental disorders to pursue studies in younger children who are still living at home. This would have the advantage of investigating problems at a time before the secondary effects of prolonged institutionalization unduly complicate the picture. We are presently hoping to survey blood 5-HT levels of children with major developmental lags who appear in the clinics during the first few years of life.

SUMMARY

Aspects of 5-hydroxyindole metabolism have been studied in some groups of mentally retarded children. Six of 23 children with the diagnosis of infantile autism had consistently elevated blood 5-HT levels. The mean level of blood 5-HT of other severely retarded children was higher than that of the mildly retarded group. No specific clinical signs could be found in these children.

We are indebted to Dr. Nicholas J. Giarman for advice regarding laboratory aspects of this

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Turner's syndrome in the male

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IN 1938, Turner[1] described 7 females whose presenting symptoms were the triad of sexual infantilism, congenital webbed neck, and cubitus valgus. It was soon recognized that sexual infantilism in females could be associated with various combinations of skeletal, cardiovascular, ocular, and other anomalies.

In 1954, Polani and co-workers[2] and Wilkins and his associates[3] noted that the nuclei of cells from patients with Turner's syndrome lacked the extramarginal chromatin particle characteristic of genetic females (i.e., they were chromatin negative). Thereafter about 80 per cent of these patients were found to be chromatin negative. It was thought that such individuals were in reality genetic males, deprived of their gonads in early fetal life, who went on to develop as phenotypic females.[4] This seemed to explain the scattered reports of Turner's syndrome in the phenotypic male as a variant of the original syndrome with incomplete destruction of the gonads.

This theory lost credence with the observation of Ford and collaborators[5] that female patients with Turner's syndrome had only 45 chromosomes with an XO karyotype presumably due to a nondysjunction during maternal or paternal gametogenesis. This observation raises the question whether the condition described as "Turner's syndrome in the male" was in fact related to "Turner's syndrome in the female" (hereafter referred to as gonadal dysgenesis).

Five phenotypic males have been seen in the Endocrine Clinic of the Children's Hospital of Philadelphia during the period 1955 to 1960 with a variety of somatic abnormalities conforming to the symptom complex of Turner's or the Bonnevie-Ullrich syndrome.

METHODS

Sex chromatin determinations were made on buccal smears with the use of a modification of the thionine staining technique of Klinger and Ludwig.[6]

The chromosome counts and karyographs were determined on leukocytes from peripheral blood by the technique of Moorhead and associates.[7]

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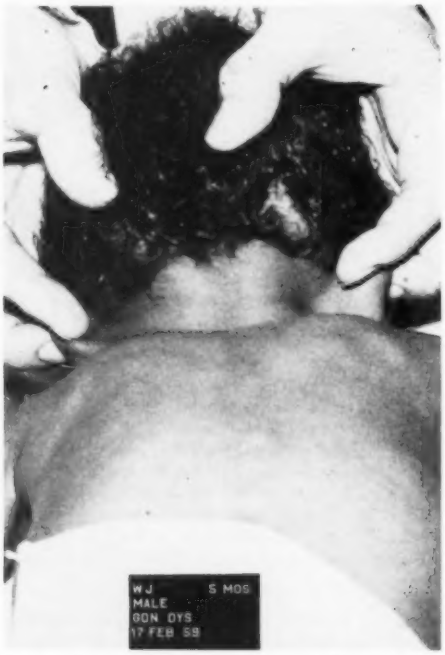

Fig. 1. Patient W. J., showing webbing of the neck.

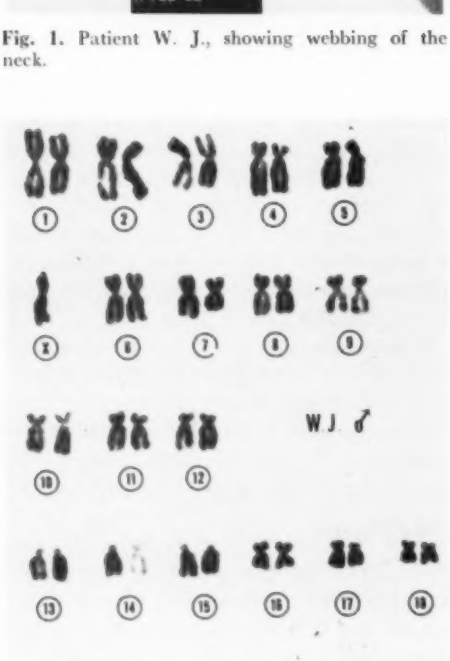

Fig. 2. Karyograph of patient W. J.

CASE REPORTS

Case 1. J. S. An 11-month-old white male child was admitted to the Children's Hospital of Philadelphia for evaluation of motor and mental retardation. He had epicanthic folds, a high arched palate, and a shield-shaped chest with pin-point nipples. His height was at the tenth percentile. Femoral pulses were palpable. He had cubitus valgus with no webbing of the neck. There was nonpitting edema of the dorsum of the hands and feet which had been present since birth. The penis measured 3.5 cm. and the testes could not be palpated. An air encephalogram showed moderate dilatation of the lateral ventricles. The sex chromatin was of the negative or male type.

Case 2. W. J. A Negro male was first seen at the age of 4½ months for evaluation of a diagnosis of "gonadal dysgenesis" (Fig. 1). He weighed 8 pounds, 7 ounces at birth. He was admitted to his local hospital at the age of 2 weeks for evaluation of excessive soft tissue around the neck. X-rays of the skull, cervical spine, and shoulders were unremarkable.

The child had a wide nasion, pug nose, low-set ears, a slightly deformed helix, webbed neck, and cubitus valgus. A Grade II late systolic murmur, which was harsh and moderately high pitched, was heard. The nipples were hypoplastic. Simian lines were present bilaterally. The penis was unremarkable but the testes, which were palpated in the inguinal canal, could not be brought into the scrotum. The sex chromatin was negative or male. The x-ray of the pelvis showed a Mongoloid type of pelvis with the iliac index significantly greater than two standard deviations below the mean expected at age 4½ months.[8] A spina bifida was present at the level of the fifth lumbar vertebra. An intravenous pyelogram was unremarkable.

The child had a bilateral orchiopexy. Biopsy revealed immature testes in relation to the age of 4½ months.

At 20 months of age he was moderately retarded in both motor and mental development. His height was at the third percentile.

The blood pressure in the arm and leg was 140/70. A systolic and early diastolic murmur at the base was present. A karyotype revealed 46 chromasomes including the XY sex chromosomes with no obvious abnormalities (Fig. 2).

Case 3. B. C. This white, male child (Fig. 3) was seen at the age of 20 months with marked pitting edema of the lower part of the lower extremities present since birth. He weighed 7 pounds, 2 ounces, at birth and was born with pitting edema of all extremities. He has had normal mental and motor development. The blood pressure was 110/80. The ears, eyes, nose, and throat were unremarkable as were the heart and lungs. The penis was slightly hypoplastic, measuring 3 cm. when stretched, and a slight hypospadias was present. The testes were both high in the canal and could be moved slightly toward the scrotum. Cubitus valgus was present, and the nipples were inverted. He was at the twenty-fifth percentile in height. The bone age corresponded to his chronologic age. X-rays of the heart and lungs were unremarkable. The sex chromatin was negative (male) and the 24 hour level of urinary 17-ketosteroids was 0.5 mg.

A bilateral orchiopexy was done at 20 months of age. Biopsy of the gonads revealed normal testes for his age. Some adrenal cortical rest tissue was present over the right epididymis.

Case 4. D. H. A $13^{10}/_{12}$-year-old white male was admitted to the Children's Hospital of Philadelphia with a 3 weeks' history of impaired speech, increased salivation, and other symptoms suggestive of a recent cerebral vascular accident presumably secondary to hypertension, which had first been noted one week prior to admission.

The developmental and past medical history were unremarkable. The blood pressure was 196/135 in each arm and was higher in the legs. He was below the third percentile in height. The eye grounds showed hypertensive retinopathy. The eyes, ears, nose, and throat were otherwise unremarkable. The neck showed webbing bilaterally. The chest appeared normal and the areolae were well formed. The external genitals were those of a preadolescent male with no pubic or axillary hair. The bone age was delayed one year. An intravenous pyelogram showed a small right kidney and an angiogram showed an aortic aneurysm involving the right renal artery which was confirmed at operation when the right kidney was removed.

A karyotype showed 46 chromosomes, including the XY sex chromosomes, to be present with no obvious chromosomal abnormalities.

Case 5. L. H. An 11-year-old white boy had been followed for 3 years because of short stature and questionable hypothyroidism (Fig. 4). His health had been good, and he was a bright child doing well in school. His growth had been progressive but consistently below the third percentile.

Fig. 3. Patient B. C., showing edema of lower extremities.

The skin was slightly mottled with a pudgy consistency. His facies was "pinched." The bridge of the nose was flat with no epicanthic folds. He had a marked cubitus valgus. The heart and lungs were unremarkable. The blood pressure was 105/68. There was no webbing of the neck. The penis was 1.5 cm. in length and the testes were small. The right testis was 1.0 by 0.5 cm. and present in the scrotum. The left testis was

Table I

Name (Ref. No.)	*Age*	*Percentile height*[25]	*Genitals*	*Webbing*	*Cubitus valgus*	*Mental retardation*	*Sexual h*
10	30	57 in.	Small testes with atrophy of left	+	+		++++
11	11	3rd	Unilateral cryptorchidism	0	+	0	+
12	21		"Navy bean" size testes	+			++
13	14		Prepubertal	+			0
14	10¼	<3rd	Testes 1.6 by 0.8 cm.	+	+	0	0
15	30	58½ in.	"Normal" testes	+	0		++++
16	36	63½ in.	"Small testes," "small penis"	0	+	+	Male escuto
17	3	<3rd	"Small"	+	+	0	0
18	13	<3rd	"Small testes"	+	+	0	0
19	10	<3rd	Normal	0	+	+	0
20a	16	10th	Cryptorchidism with small right testes	+		0	Male escuto
20b	19	63½ in.	Hypospadius, cryptorchid, left testes	+		0	Male escuto
21	16	68 in.	Cryptorchidism	0	+	0	Male escuto
22	21		Testes ⅓ normal size	+	+		Male escuto
23	7	<3rd	Cryptorchidism	+	+	0	0
24	2¼	<3rd	Small penis, hypospadius	+		+	0
This study:							
Case 1	11 mo.	10th	Cryptorchidism	0	+	+	0
Case 2	20 mo.	3rd	Inguinal testes	+	+	+	0
Case 3	3	25th	Cryptorchidism	0	+	0	0
Case 4	13 10/12	<3rd	Prepubertal	+	0	+	0
Case 5	11	<3rd	Testes 1.0 by 0.5 cm.	0	+	0	0

[a], Low-set ears and/or anomaly of ear lobe.
b, Low hairline.
c, Epicanthic folds.
d, Ptosis.
e, Shieldlike chest and/or hypoplastic nipples.
f, Hypoplastic mandible.
g, Wide nasion.
h, Simian line.
i, Edema of dorsum of hands or feet.
j, High arched palate.
k, Strabismus.
l, Decreased libido.
m, Eunuchoid appearance.

by 0.2 cm. and fixed high in the inguinal canal. The consistency of the left testis was abnormally firm. The bone age was retarded about 2 years. The protein-bound iodine was 4.4 μg per cent; the butanol extractable iodine was 3.9 μg per cent. The radioactive iodine uptake was 19.5 per cent at 24 hours. The chromatin smear was negative (male). Urinary excretion of 17-ketosteroids was 4.1 mg. per 24 hours. A biopsy of the

Sexual hair	*Cardiovascular anomalies*	*17-KS*	*FSH*	*Testes biopsy*	*Other anomalies**
++++	No coarctation	9, 11.9		Azospermia with hypoplasia of seminiferous tubules	
+		1.2	4.1		e, r
++		6.2	6-105	Hypoplasia of tubules	a, j, m, n, p
0			<12		c, e, j
0	Systolic murmur at apex	0.6	"Low"	Retarded germinal epithelium	b, c, q, t
++++	B.P. 145/75	5.9	96		t
Male escutcheon		11.1	180	Small seminiferous tubules	l, o, r, y
0	Murmur	0.55	80		d, f, s
0	Right aortic arch, sys. and dias. murmur	2.6	64	Arrest of spermatogonia. No maturing interstitial cells	c, e, k, q
0	None	1.5	50		v, z
Male escutcheon	Enlarged heart, sys. and dias. murmur		52.8		a, b, c, e, f, i, j, z
Male escutcheon	Systolic murmur		24.6		a, f, i, j
Male escutcheon	None	7.3	52		s, t, u
Male escutcheon					b, q, r, s, w
0	None	1.1	6	"Infantile testes"	b, d, f, s
0	Grade III systolic murmur	1.6	3.5		a, b, x
0	B.P. 110/68				e, i, j
0	B.P. 140/70, systolic murmur			Immature testes for age	a, b, c, e, g, h, s
0	None	0.5		Normal for age	i
0	Aneurysm of descending aorta				a
0	None	4.1		Right testes normal	j

n, Microophthalmus.
o, Goiter.
p, Facial palsy.
q, Scoliosis and/or kyphosis.
r, Cervical spine anomalies.
s, Spina bifida.
t, Osteoporosis.
u, Cervical rib.
v, Premature cranial stenosis.
w, Claw feet.
x, Hypermobility of joints.
y, Gynecomastia.
z, Funnel chest.

Fig. 4. Patient L. H., showing short stature, cubitus valgus, and peculiar facies.

right testis was normal for his age. The left testis was severely atrophic.

DISCUSSION

"Turner's syndrome in the male" can best be appreciated in its historical context. Turner's[1] observation of the association of sexual infantilism with the multiple congenital anomalies of Bonnevie-Ullrich was quickly accepted as an established syndrome in the phenotypic female. It soon became apparent that there were many clinical variants of this syndrome. The two most constant features were sexual infantilism and short stature.[9] Other clinically recognized anomalies, such as webbed neck, cubitus valgus, coarctation of the aorta, facial anomalies, etc., were present in various combinations and degrees.[9] The absence of many of these stigmas has been emphasized in this clinic by the observation of a short prepubertal girl, normal in all other respects, who revealed a negative sex-chromatin pattern.

It does not seem surprising, on hasty reflection, that this syndrome might occur in the phenotypic male. Indeed, case reports of "Turner's syndrome in the male" soon appeared, but the number was considerably less than of those in the phenotypic female. Sixteen cases in males have been culled from the literature.[10-24] On review of the 5 cases described above plus the 16 cases from the literature, it appears that the diagnosis of Turner's syndrome in the male is somewhat nebulous in that it is not supported by objective evidence of a chromosomal disorder. A summary of anomalies associated with this syndrome is outlined in Table I.

All male patients have had various combinations of congenital anomalies comparable to those associated with gonadal dysgenesis. Of these, webbing of the neck and/or an increased carrying angle of the elbow (i.e., cubitus valgus) have been most common. These anomalies alone would be noteworthy, yet other malformations were always present.

A height at or below the 25th percentile was present in 17 of 18 patients. Facial anomalies of one sort or another were present in 13 of 21 of these patients. Mental retardation was noted to be present in 6 of 16 of these patients. Cryptorchidism, unilateral or bilateral, was present in 7 of 21. Sexual infantilism in the 8 postpubertal males, an almost constant feature in the female, was not observed. However, 7 of these 8 males had small testes and/or cryptorchidism, a remarkable coincidence which defies explanation at present. It would be interesting to ascertain their reproductive history. In the 9 instances where a biopsy was obtained, histologic examination revealed testicular tissue with variable degrees of hypoplasia of tubular structure. In the 8 patients in whom the crude chromatin sex pattern was determined, all were "chromatin negative." A bone age determination was made in 9 cases and in 2 there

was a significant delay in bone maturation. Admittedly, the clinical tableau tempts one to designate these cases as a clinical syndrome akin to gonadal dysgenesis. Were one to insist upon a close relationship between these two conditions, a common factor other than the recognized chromosomal factor need be involved. Such an element is at present elusive.

Unfortunately, in Turner's syndrome in the male, a clear-cut, morphologic, unifying basis of an etiological mechanism is lacking. Of the 2 patients (Cases 2 and 4) described above, whose chromosomes were studied in detail by a karyograph, both had total chromosome counts of 46 without recognizable chromosomal abnormalities. This is in agreement with the 7 cases of Turner's syndrome in the male in which chromosome counts were reported by Court Brown and associates.[26] It appears that a chromosomal abnormality analogous to the XO karyotype associated with gonadal dysgenesis in the female is not present in the male in Turner's syndrome. Many somatic anomalies, however, are shared by the two syndromes. This suggests that the chromosomal abnormality (i.e., the lack of a sex chromosome) found in most cases of gonadal dysgenesis is not solely, if at all, responsible for the many somatic deformities seen in the female.

In retrospect, the symptom complex described as Turner's syndrome in the male is found to occur in a rather heterogeneous group of patients. As in gonadal dysgenesis, multiple congenital anomalies are present in various combinations and degrees. The concept of a forme fruste implies a well-defined complete syndrome. A reasonably complete syndrome has been found sufficiently often in gonadal dysgenesis to make it possible to recognize the less complete forms of this entity. Furthermore, the delineation of the latter can be supported by chromosomal analysis. A reasonably complete form, with several associated classical anomalies, if there is such an entity, has not been described for Turner's syndrome in the male. The validity of designating such a loose and variable symptom complex as Turner's syndrome in the male is questioned pending further objective evidence of a chromosomal derangement not apparent by current methods of study.

The observations that certain symptom complexes are associated with chromosomal anomalies are intriguing.[27-30] Mongoloid children not only have a rather characteristic extra autosome[27] but share as well some of the anomalies found in male Turner's syndrome in the male such as low-set ears, epicanthic folds, low hair line, mental retardation, high arched palate, etc. The patient described by Edwards and associates[28] had an extra autosome different from that of Mongolism, and shared with Turner's syndrome in the male such anomalies as webbing of the neck, low-set ears, and mental retardation. Other anomalies were present as well. Our Case 2 was in some notable respects Mongoloid and yet did not demonstrate the chromosomal anomaly described in this condition.[27]

Ferguson-Smith and co-workers[30] described a patient with an XXXY sex-chromosome constitution. There were webbing of the neck, small testes, mental retardation, and other anomalies.

Thus, similar congenital anomalies or groups of congenital anomalies may be associated with different varieties of chromosomal aberrations. Or, as in male Turner's syndrome in the male, no gross recognizable chromosomal aberration may be observed. We would question whether Turner's syndrome in the male is in reality a specific diagnosis rather than a collection of certain variable congenital anomalies of multiple etiology. The similarity, in some instances, to gonadal dysgenesis raises the question implied above: Are the multiple somatic anomalies in the latter the result of an absent sex (X or Y) chromosome?

SUMMARY

1. Five patients with the symptom complex described as Turner's syndrome in the male are presented. Sixteen additional cases have been collected from the literature. The associated anomalies are summarized.

2. Chromosomal counts in 2 of our patients showed the diploid number of 46 without recognizable abnormalities. This is in accord with other reports.

3. It is suggested that the so-called Turner's syndrome in the male is not a well-defined entity supported by objective chromosomal aberrations. Rather, it may represent several loosely related clinical conditions of unknown etiology. The marked clinical similarity, in some instances, to gonadal dysgenesis may signify that the somatic anomalies in the latter are not clearly attributable to the observed chromosomal defect.

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The chromosome studies contained in this report were performed by Dr. P. S. Moorhead, Wistar Institute of Anatomy, Philadelphia, Pennsylvania.

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Cardiac failure in infancy

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CARDIAC failure in an infant is a relatively common pediatric emergency. This study records the findings in 115 consecutive cases of cardiac failure in infants under 2 years of age seen on the pediatric service of the Medical College of Virginia Hospitals between January, 1953, and January, 1960.

Detailed studies of cardiac failure in children of all ages have been presented by Keith,[1] who recorded a mortality rate of 85 per cent in 304 children; most of the deaths occurred in the first years of life. Nadas and associates[2] have been concerned with the therapeutic aspects of cardiac failure. More recently Blumenthal and Anderson[3] reported a mortality rate of 67 per cent in children under 1 year of age, and Simpson[4] in England, one of 48 per cent. Catherine Neill's excellent monographs[5, 6] emphasize the necessity of exact diagnosis of the underlying cardiac lesion as soon as emergency measures for cardiac failure have been effective. In the child with a congenital heart lesion, the occurrence of cardiac failure often is an indication for as prompt surgical repair as possible.

PLAN AND PURPOSE

One hundred and fifteen patients under 2 years of age met the criteria for cardiac failure. Major manifestations required for inclusion of the infant in the study were dyspnea, cardiac enlargement, tachycardia, or hepatomegaly. Dyspnea was always present, and cardiac enlargement as determined by roentgenography or at necropsy was noted in all but a few cases, as was hepatomegaly. The term, cardiac failure, is used here to indicate that the heart has failed to maintain adequate output to supply the metabolic needs of the body. It is generally agreed that both forward and backward failure play important roles in the clinical syndrome. The recent study of Blumenthal and Anderson[3] gives a detailed discussion of the pathologic physiology in infants with cardiac failure.

The purpose of this study is to emphasize the serious prognosis of congestive heart failure in infancy and to stress the importance of early definitive diagnosis. Emphasis will be placed on conditions which are potentially remedial through medical or surgical care. The major causes of heart failure in infants under 2 years of age together with their prime manifestations will be tabulated in each category.

RESULTS

Primary causes of congestive cardiac failure in the current study are listed in Table I. Seventy-one per cent of the cases were in one of the first six categories, namely, endomyocardial disease, interventricular septal

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Table I. Etiology

1. Endomyocardial disease		30
2. Interventricular septal defect		13
3. Coarctation		12
4. Transposition		11
5. Patent ductus arteriosus		9
6. Aortic atresia		7
7. Atrioventricular canal defect		4
8. Tricuspid atresia		4
9. Truncus arteriosus		3
10. Arrhythmias		3
11. Anemia		3
12. Interatrial septal defect		3
13. Miscellaneous		13
Dextrocardia and other lesions	2	
Anomalous pulmonary venous return	2	
Single ventricle	3	
Hypoplastic left ventricle	2	
Cor biloculare	1	
Rheumatic fever with mitral insufficiency	1	
Pulmonary stenosis	1	
Acute glomerulonephritis	1	
Total		115

defect, coarctation of the aorta, transposition of the great vessels, patent ductus arteriosus, and aortic atresia. In Fig. 1, the frequency of the congenital lesions is shown according to age at the onset of failure. It is noteworthy that symptoms in aortic atresia appear frequently in the first week of life; in the succeeding weeks, one is more apt to encounter those resulting from coarctation, transposition, and interventricular septal defects.

Fig. 2 shows the mean onset of failure in endocardial fibroelastosis at 5 weeks in contrast to failure in the myocarditis group appearing chiefly after 6 months of life.

Fig. 3 lists the relative frequency of major signs and symptoms on which the diagnosis of failure was made. Dyspnea was evaluated by comparison with normal respiratory rates for a given age. Tachycardia was defined as a pulse rate greater than 150 per minute; it occurred in approximately two thirds of all cases. The remainder had cardiac rates between 130 and 150. This can be observed correctly only when the child is sedated or asleep. The liver was considered to be abnormally enlarged when it was more than 2 cm. below the right costal margin in the midclavicular line. The rapidly changing size of the liver in cardiac failure is striking.

During the study, 9 infants with pneumonia were considered to have congestive heart failure and were given digitalis therapy. After careful review of their clinical course, roentgenograms, and electrocardiograms, they were excluded from the study, primarily because of the absence of cardiomegaly. The finding of pulmonary râles in two thirds of the cases may reflect both congestive and infectious lesions which are frequently superimposed. Peripheral edema occurred in only one fourth of the cases, much less than the usual incidence in adults. Associated findings of gallop rhythm, cyanosis, slow development, poor weight gain, or sudden excessive weight gain are supportive but not diagnostic features.

The electrocardiogram is a useful tool in the diagnosis of the underlying cardiac lesion but there is no single pattern for cardiac failure. The S-T and T changes, often with enlarged P waves, in the endomyocardial diseases were considered to be diagnostic. Interventricular septal defects and patent ducti showed combined left and right ventricular strain patterns in contrast to atrial defects; all infants with such lesions had right heart strain with the typical rSR′ in V_1 and V_3R. Patients with tricuspid atresia had left axis deviation in the limb leads and a predominant S over R in V_1. The exact opposite was found in relation to pulmonic stenosis. The electrocardiogram was diagnostic for arrhythmias and dextrocardias, but was less specifically helpful in other

Table II. Plan of digitalization for infants under 2 years of age

Drug	*Route*	*Total digitalizing dose*	*Maintenance daily dose*
Cedilanid	Intravenous	0.02 to 0.03 mg./lb.	
Lanoxin	Intravenous, intramuscular or oral	< 5 lb., 0.04 mg./lb. > 5 lb., 0.03 mg./lb.	¼ total digitalizing dose
Digitoxin	Intravenous or oral	0.02 to 0.03 mg./lb.	1/10 total digitalizing dose

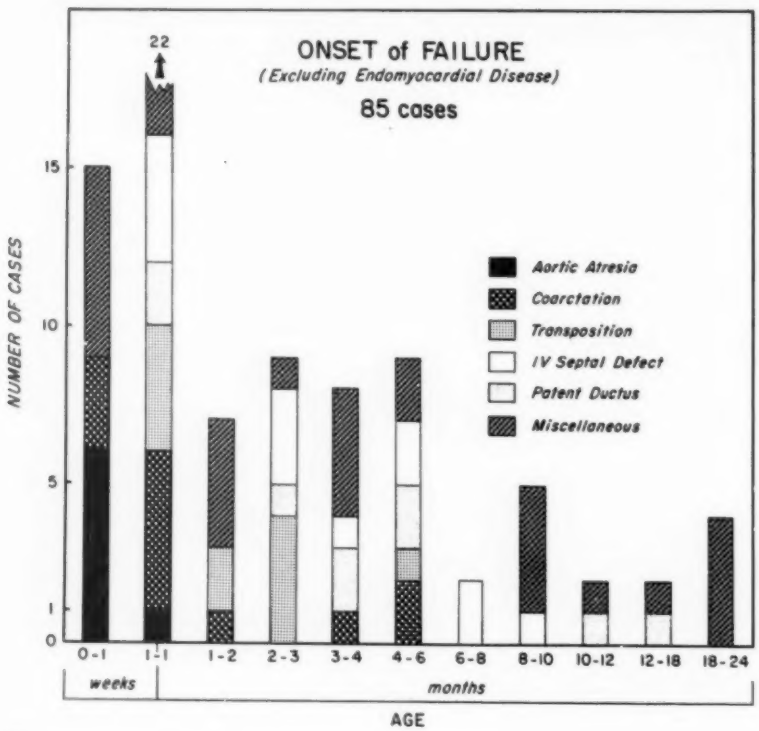

Fig. 1.

lesions. In all cases, it is necessary to obtain tracings before digitalization.

Cardiac catheterization was of primary assistance in cases of left-to-right shunt and was performed in 25 cases, whereas angiocardiograms were used in 11 infants with right-to-left shunts who were grossly cyanotic. Retrograde aortograms, valuable in the diagnosis of patent ductus or coarctation, were obtained in 19 cases.

GENERAL THERAPY

The following therapeutic principles and/or measures constituted the initial management:

1. Oxygen was administered by tent or in an Isolette to keep the infant cool and comfortable.

2. Rest is not easy for an apprehensive, dyspneic child. Reassurance, a mother nearby, and often mild sedation help. If pulmonary edema occurred, an orthopneic position and morphine sulfate, 0.1 mg. per pound, were used.

3. Antibiotics were administered when infections complicated the pulmonary problem.

4. Low salt diets were advised; occasionally Lonalac was used.

5. Diuretics were given to selected cases, notably Mercuhydrin intramuscularly in a dosage of 0.1 to 0.2 c.c.

6. Digitalis was begun in 92 cases as soon as the diagnosis was made and an electrocardiogram had been obtained. In critical cases, intravenous desacetyl lanatoside C (Cedilanid) was administered; half the total digitalizing dose was given at once, and a quarter of it at hourly intervals for 2 doses. This drug is rapidly excreted and digitalization with a longer-acting preparation must follow within 4 to 8 hours.

A safer and more commonly used preparation, digoxin (Lanoxin), was given in the dosage listed in Table II. The drug may be

given intravenously, intramuscularly, or orally. Its lower range of toxicity, quick absorption, and rapid excretion make it useful in this age group. Hauck, Ongley, and Nadas[7] were impressed with its advantages.

For those preferring a longer-acting preparation, digitoxin is available. Two cases of digitalis intoxication occurred. One infant with coarctation of the aorta received 0.3 mg digitoxin instead of 0.03 mg. as ordered and developed a 2:1 block, but recovered following administration of potassium-containing fluid. Another child with myocarditis received the correctly calculated dose but showed evidence of toxicity. Slightly lower dosage is advisable in this group as they are often more susceptible to ventricular premature beats and other signs of toxicity.

CONGENITAL DEFECTS

Coarctation of aorta. Special attention should be given to infants with defects that are remedial. Coarctation of the aorta was found in 12 patients, 8 males and 4 females. All presented in failure under 6 months of age. Dyspnea was always prominent as were an enlarged liver and elevated blood pressure in the arm. Four infants died shortly after admission; the diagnosis was made at necropsy. Of the 8 who were more carefully studied clinically, the mean arm systolic blood pressure was 167 mm. Hg. Two of these 8 were of the infantile type of coarctation; both had weak but palpable femoral pulses and an arm systolic blood pressure 40 mm. Hg higher than that in the legs. Of the 6 with adult type of coarctation, only one had palpable femoral pulses; this child had a differential of 60 mm. Hg between the arm and leg. Experience is necessary to obtain accurate blood pressures in infancy, but accurate data can be diagnostic of coarctation of the aorta.

Eight of the infants with coarctation of the aorta were cyanotic during the acute stage of failure. Four had been premature at birth. Table III shows the other major findings. Of the 9 who received digitalis, 7 had a loss of weight of 3 to 8 ounces within 48 hours. The clinical relief of dyspnea and reduction of liver size were more satisfactory means of evaluating therapy.

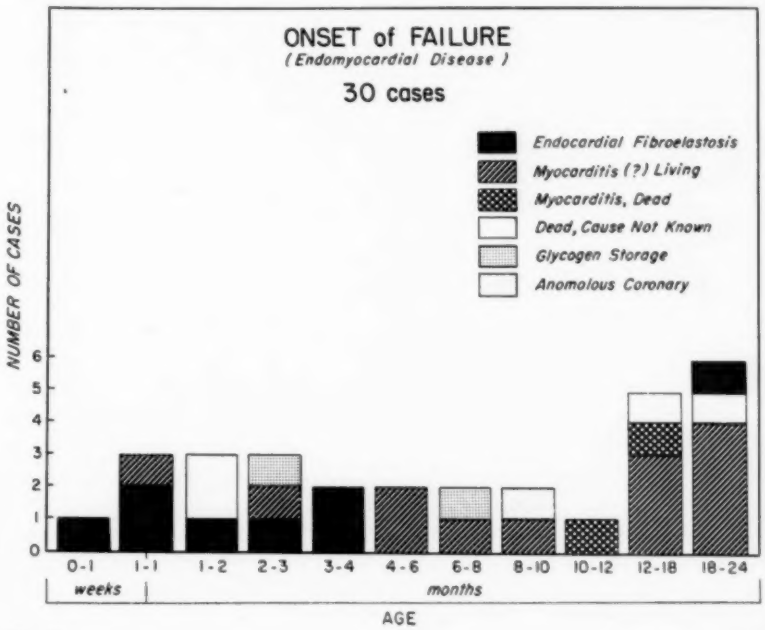

Fig. 2.

Table III

Diagnosis	*Total*	*Race*		*Sex*		*Onset of failure (months)*			*Dyspnea*	*Pulse > 150*	*Liver > 2 cm.*	*Cardiac enlargement by x-ray*	*Cyanosis*	*Râles*	*Edema*
	No. cases	*White*	*Negro*	*Male*	*Female*	*Min.*	*Max.*	*Mean*							
1. Coarctation of aorta	12	7	5	8	4	1/30	6	1	12	8	12	12	8	11	
2. Patent ductus arteriosus	9	5	4	2	7	1/3	18	4	9	8	9	9	2	5	
3. Interventricular septal defect	13	8	5	5	8	½	10	3	13	10	8	13	2	4	
4. Transposition of great vessels	11	5	6	8	3	1/3	5½	1½	11	8	7	10	11	2	
5. Aortic atresia	7	6	1	4	3	Birth	½	1/15	7	4	5	4	7	1	
6. A-V communis	4	3	1	3	1	½	10	6¾	4	1	3	2	3	2	
7. Tricuspid atresia	4	2	2	2	2	Birth	20	1	4	1	4	4	4	2	
8. Interatrial septal defect	3	2	1	2	1	¼	1	1/3	3	1	2	2	3	2	
9. Truncus arteriosus	3	1	2	2	1	1/15	1	1/6	3	2	3	3	2	2	
10. Arrhythmia	3	2	1	2	1	¾	1¾	1¼	3	3	2/2	1/1	2	0	
11. Anemia	3	0	3	2	1	9	20	19	3	2	3	1/1	0	2	
12. Endomyocardial disease	30														
a. Myocarditis (clinical)	13	3	10	6	7	½	24	14	13	6	13	13	5	13	
b. Myocarditis (necropsy)	2	0	2	0	2	12	17	—	2	1	2	2	1	2	
c. Fibroelastosis (necropsy)	8	5	3	2	6	Birth	24	2	8	6	7	8		6	
d. Glycogen storage disease	2	1	1	2	0	6	7½	—	2	1	2	2	1	2	
e. Anomalous coronary artery	1	0	1	1	0	—	—	9	1	1	1	1	0	1	
f. Died—no necropsy	4	1	3	1	3	1½	24	8	4	2	4	4	3	4	
13. Miscellaneous	13														
a. Dextrocardia plus associated lesions	2	1	1	1	1	¾	9	—	2	1	1	2	1	2	
b. Anomalous pulmonary venous return	2	2	0	1	1	1	2	—	2	2	2	2	2	1	
c. Cor biloculare	1	1	0	1	0	—	—	2½	1	1	1	0	1	1	
d. Single ventricle	3	2	1	1	2	4	11	5	3	3	2	3	1	2	
e. Pulmonic stenosis	1	1	0	0	1	—	—	3¾	1	0	1	1	1	1	
f. Rheumatic fever	1	0	1	0	1	—	—	22	1	1	1	1	0	0	
g. Acute glomerulonephritis	1	0	1	1	0	—	—	18	1	1	1	1	0	1	
h. Hypoplastic left ventricle	2	1	1	1	1	2½	4½	—	2	1	2	2	2	1	
Total	115	59	56	58	57	Birth	24	—	115	75	98	103	62	71	27

The electrocardiograms varied greatly, with 3 showing right cardiac strain, one left, and one combined; almost all had S-T segment and T wave changes. Where a diagnosis is not clear clinically, retrograde aortograms are the most satisfactory method of confirmation; they were performed in 6 cases. An example is shown in Fig. 4 of a case which could not be controlled on digitalis alone; and therefore, a surgical repair was performed. Unfortunately, the child died a month later with bronchopneumonia. Another child, whose coarctation was successfully repaired at the age of 2 years,

Cyanosis	Râles	Edema	Murmur: Sys.	Murmur: Diast.	Abnormal ECG	Special studies: Catheterization	Special studies: Aortogram	Special studies: Angiogram	Digitalis	Operation: No.	Operation: Living	Age at death (months): Min.	Age at death (months): Max.	Age at death (months): Mean	Necropsy (deaths)	Case fatality rate
8	11	3	8	–	9	0	6	0	9	3	1	1/30	24	1¼	7/8	8/12
2	5	1	9	5	5	2	6	0	5	5	3	6	36	–	2/2	2/9
2	4	1	13	–	9	9	4	1	13	3	0	2½	10½	6¾	4/6	6/13
11	2	2	9		7	2	0	4	8	4	0	½	9	3	10/11	11/11
7	1	1	2		2/3	0	0	1	3	0	–	1/15	1	1/10	7/7	7/7
3	2	1	3		3	1	0	0	4	1	0	½	32	11	4/4	4/4
4	2	1	2	–	3	2	0	3	3	2	0	1¼	2½	2	3/4	4/4
3	2	1	1		2/2	0	0	0	2	0	–	⅓	1	–	2/2	2/3
2	2	0	3		1/1	0	0	0	3	0	–	1/15	2½	1/6	3/3	3/3
2	0	0	0	0	3	0	0	0	3	0	–	–	–	–	0	0/3
0	2	1	1	–	0	–	0	0	3	0	–	19	20½	–	1/2	2/3
5	13	6	0	0	13	2	0	0	13	0	–	–	–	–	0	0/13
1	2	1	0	0	1/1	0	0	0	1	0	–	12	17	–	2/2	2/2
	6	5	(1 soft sys.)		7/7	1	0	1	3	0	–	1	54	2	8/8	8/8
1	2	1	(1 soft sys.)		2	0	0	0	2	0	–	8½	9	–	2/2	2/2
0	1	0	0	0	0	0	1	0	1	1	0	–	–	52	1/1	1/1
3	4	2	0	0	4	1	0	0	4	0	–	1¾	30	15	0/4	4/4
1	2	0	2	0	2	0	0	0	1	0	–	–	–	1	1/1	1/2
2	1	0	2	0	2	1	0	0	2	1	0	1	3½	–	2/2	2/2
1	1	0	1	0	1	0	1	0	1	0	–	–	–	4	1/1	1/1
1	2	0	2	0	1/1	3	0	1	3	2	1	–	–	13	1/1	1/3
1	1	0	1	–	1	0	0	0	1	1	0	–	–	4	1/1	1/1
0	0	0	1	1	0	0	0	0	1	0	–	–	–	–	0	0/1
0	1	0	0	0	1	0	0	0	1	0	–	–	–	–	0	0/1
2	1	0	2	–	1/1	1	1	0	2	1	–	6	35½	–	2/2	2/2
62	71	27	62	6	80	25	19	11	92	24	5	1/30	54	–	64/74	74/115

now 6 years of age and has normal leg blood pressures (Fig. 5). Three children whose hearts were well compensated on digitalis between the ages of 1 and 4 years will have surgical repair later. Maintenance of the child on digitalis is desirable if failure is to be controlled until he attains an optimum age for operation, usually about 6 to 8 years.

Eight (66 per cent) of these infants died at a mean age of 5 weeks; seven were examined at necropsy. It is interesting that 4 had an associated open ductus of the infantile type. Other congenital defects were

common and included cerebral defects, webbed neck, and defects of the kidney and digits.

Patent ductus arteriosus. Patent ductus arteriosus was the underlying lesion in 9 infants (7 females) who developed cardiac failure at a mean age of 4 months. The specific findings are listed in Table III. All had dyspnea, hepatomegaly, and cardiac enlargement with pulmonary congestion. The murmur was machinery in type (M) in 5 and only systolic (S) in 4. The murmurs are related to their ages as follows:

Age in months:	⅓	2	3	4	6	12	18
Murmur:	S	M	S	S	M	S	M
				M			
				M			

A history of rubella in early pregnancy was obtained from the mothers of 4 infants, 3 of whom had congenital cataracts. The common association of patent ductus in an infant to rubella in the mother during early pregnancy has been noted by many authors.[8]

Pulse pressures averaged 60 mm. Hg in 6 patients whose auscultatory blood pressures were considered to be satisfactory. Electrocardiograms showed no ventricular preponderance in 4 but were grossly abnormal in 5; one of them showed right and 2, left preponderance. Two had patterns of bilateral strain. The retrograde aortogram can be of great assistance when the clinical findings are atypical; this was performed in 6 infants.

At the time of this writing, 7 children are living of whom 3 have had successful surgical repair. These children have been followed for an average period of 3 years.

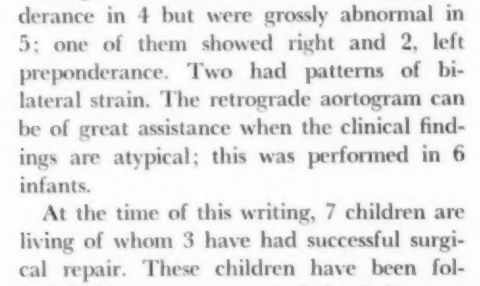

Fig. 3.

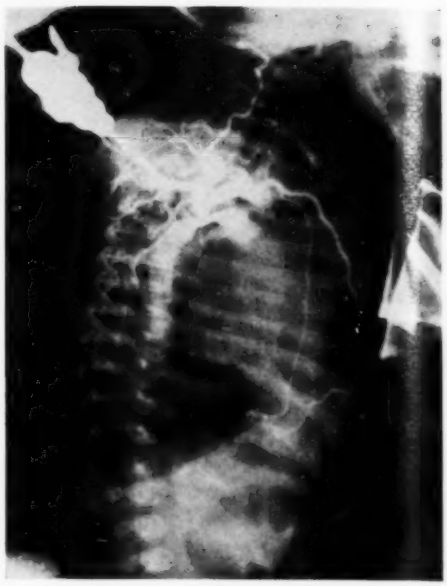

Fig. 4. Retrograde aortogram. Coarctation of aorta and large patent ductus arteriosus.

Operation is planned within the next few months for the 4 children under 14 months of age who are now doing well on digitalis therapy. Necropsy was obtained on 2 patients who died postoperatively. A report has been published of one child of 2½ years who had, in addition to the ductus, a coronary artery fistula; both were repaired surgically.[9] The other infant died at 6 months of age with pneumonia and severe pulmonary hypertension 2 days after surgical ligation.

A patent ductus should be repaired at any age if cardiac failure cannot be controlled. The youngest of our infants to have a successful repair was 5 months old. This child was in failure at 2½ weeks, at 4 months, and at 5 months of age, and responded to digitalis by a weight loss of 5 to 8 ounces each time.

Interventricular septal defect. A defect in the interventricular septum is one of the more frequent causes of congestive failure in infancy. The present series includes 13 cases, or 11 per cent of the total. Failure occurred at a mean age of 3 months. A murmur of moderate intensity or greater was

Table IV. Cardiac failure associated with anemia

Patient	Diagnosis	Hb	Treatment	Remarks
9 month Negro female	Sickle cell crisis	1.8 Gm. %	Transfusion 32 c.c., later 50 and 80 c.c. packed cells; also Cedilanid	Living
19 month Negro male	Iron deficiency anemia	2 Gm. %	50 c.c. whole blood twice and 600 c.c. fluid intravenously	Died with pulmonary edema and cardiomegaly
20 month Negro male	Sickle cell crisis	1 Gm. %	150 and 200 c.c. whole blood transfusion and 200 c.c. fluid intravenously	Died in pulmonary edema

noted in all cases. Table III shows detailed findings in this group and the succeeding ones.

With congestive failure in infancy, this lesion has a poor outlook, the mortality being 46 per cent in this series. At present, interventricular septal defects are being corrected with the use of open heart procedures, but the case fatality rate in infancy is much higher than in later childhood. Open heart surgery was performed in 3 infants of the present series who were doing very poorly; each one died postoperatively. Sirak,[10] Gasul,[11] Neill,[6] and others mention the poor operative risk with open heart surgery for this condition under the age of 2 years. These infants stand a better chance of survival with medical care until they are older than they do with currently available surgical techniques.

Transposition of great vessels. Complete transposition of the great vessels is the most frequent cyanotic lesion causing congestive failure in infancy. These infants are characteristically ill from birth and become cyanotic very early. In our 11 cases, cardiac failure occurred at a mean age of 1.5 months, and all had marked cyanosis before this time. Nine were noted to have murmurs of moderate intensity and pulmonary congestion. A typical roentgenogram is shown in Fig. 6. Of the 7 abnormal electrocardiograms, 6 showed right ventricular hypertrophy. All 11 patients with this diagnosis died, the oldest one living to 9 months of age.

This problem is a challenge to the surgeon, but at the present time the mortality risk is high. Recent reports of surgical repair by Senning[12] in Sweden and Baffes[13] in Chicago gave a ray of optimism which led to attempts at correction. These were unsuccessful in the 4 infants in whom surgical repair was attempted in this series.

Aortic atresia. Although aortic atresia is an infrequent anomaly, it accounts for a major portion of the cases of congestive failure in the first week of life. Infants may appear well at birth; but in our 7 infants the mean time for onset of failure was at 2 days of age. Three infants had evidence of cardiac failure before 24 hours of age. All were cyanotic but only 2 had significant murmurs. Surgical correction is not possible at present. The mean age at death was 3 days; only one infant lived as long as 4 weeks.

Atrioventricular canal defects. Four infants with a persistent atrioventricular canal

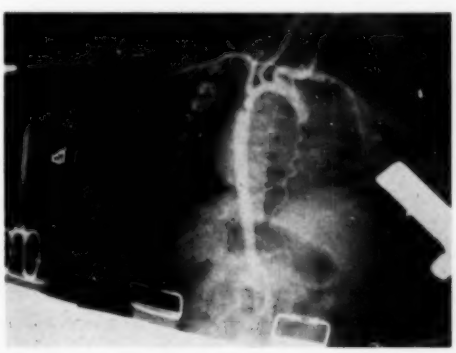

Fig. 5. Retrograde aortogram. Coarctation of aorta.

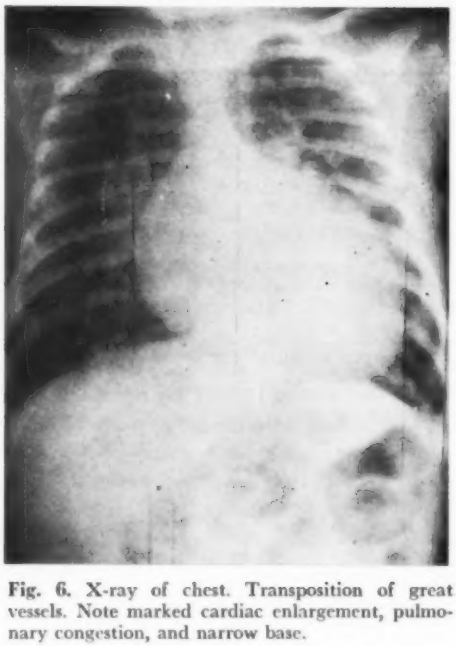

Fig. 6. X-ray of chest. Transposition of great vessels. Note marked cardiac enlargement, pulmonary congestion, and narrow base.

had congestive failure with the onset at the mean age of 7 months. The electrocardiogram assumes a major role in this diagnosis, the basic pattern consisting of left axis deviation in the limb leads with partial or complete right bundle branch block in the precordial leads. These patients are poor risks and are not likely to survive long on medical therapy. The surgical case fatality rate is high; but surgery is justified in selected cases.

Tricuspid atresia. Tricuspid atresia may also cause left ventricular failure, which was noted at a mean age of 1 month in the 4 cases in this series. Prominent diagnostic features were cyanosis and left ventricular strain. The mean age at death was 2 months. Operation is associated with a high mortality; and, for the present, conservative management is advisable unless severe anoxic spells require a shunt procedure.

Miscellaneous congenital defects. Interatrial septal defects of the ostium secundum type accounted for 3 cases of congestive failure; two infants died quickly at less than 1 month of age. One is living 15 months after the acute episode of congestive failure.

Total anomalous pulmonary venous return was observed in 2 infants; in one the veins entered the right atrium proper and in the other they returned to the coronary sinus. As soon as the diagnosis is clear, corrective open heart surgery should be carried out, although results are far from satisfactory at present. The figure-of-eight contour noted on the chest roentgenogram and the electrocardiogram are helpful diagnostic features. Cardiac catheterization with dye curves is indicated prior to operation.

Pure pulmonic stenosis is a rare but potentially remediable cause of failure in infancy. One typical case was seen in the present study. Increasing cyanosis and dyspnea, a harsh systolic murmur and thrill at the base, severe right ventricular strain, cardiac enlargement, hepatomegaly, and clear lungs were found in an infant at 6 months of age. Digitalis was given for 6 hours, but the failing right ventricle did not tolerate emergency surgery.

Other anomalies found to cause congestive failure in infancy are listed in Table I and Table III. Attempt at surgical correction has little to offer for these lesions at the present time.

INFECTIONS

The occurrence of rheumatic fever with mitral insufficiency in a 22-month-old Negro female was of interest because of the early age at onset. No murmur had been heard 6 months previously, but one was discovered by her family physician just before admission. Cardiomegaly and an apical systolic and diastolic murmur with clinical evidence of congestive failure supported the diagnosis. Laboratory studies revealed a sedimentation rate of 34 mm. in 1 hour, an antistreptolysin titer of 250 Todd Units, and a C reactive protein of 4 plus. The electrocardiogram had no rSR′ pattern. There was a good response to therapy with digitalis and a corticosteroid. Eighteen months later she has a murmur typical of rheumatic mitral insufficiency.

An 18-month-old Negro male was admitted with hypervolemic cardiac failure with findings typical of acute glomerulonephritis. No murmur was noted. He improved on digitalis and other conservative therapy and is doing well 6 months later.

ARRHYTHMIAS

One female and two male infants presented under 4 months of age with supraventricular tachycardia. All had cyanosis, dyspnea, hepatomegaly, and heart rates between 245 and 300 per minute. The diagnosis was confirmed by electrocardiographic examination. One has been readmitted 3 times with recurrent episodes of paroxysmal tachycardia; interim electrocardiograms show changes characteristic of the Wolff-Parkinson-White syndrome. None of them have significant murmurs. All responded promptly to digitalis and are living; they have been followed for an average of 2 years. Nadas[14] has shown that such excessive heart rates are not well tolerated by infants, and that 50 per cent of affected infants will develop cardiac failure within 36 hours. We have maintained our patients on digitalis therapy for at least one year.

ANEMIA

Anemia is an uncommon primary cause of congestive cardiac failure but is an aggravating factor to an existing cardiac lesion. Hypoxia associated with anemia causes disturbed myocardial function and an increased work load on the heart. Table IV shows the data from 3 cases without heart disease but with hemoglobin levels between 1 and 2 Gm. per cent. Two infants with sickle cell anemia and aplastic crises and one with severe iron deficiency anemia are presented. Digitalization is of less value than small, packed red blood cell transfusions.

The formula of Rutzky[15] is valuable in calculating the maximal volume of packed cells for one transfusion. Except in the case of acute blood loss, 3 c.c. per pound is given when the hemoglobin concentration is 3 Gm. per cent; 4 c.c. per pound when it is 4 Gm. per cent; and 5 c.c. per pound when it is 5 Gm. per cent. At levels of hemoglobin of 1 to 2 Gm. per cent, the same ratio may be used if the child is under 2 years of age. Our infants who died in 1953 and 1954 were given too much blood and far too much fluid. Packed cells are preferable and if given in increments at intervals of 12 to 24 hours, these children should be salvageable as was the recent one recorded in Table IV. Cardiac capacity is severely limited so that only small transfusions should be given if fatal pulmonary edema is to be avoided.

PRIMARY ENDOMYOCARDIAL DISEASE

Thirty patients presented with large hearts and cardiac failure without a significant murmur or blood pressure changes; the diagnostic categories are listed in Table III.

As a group the 8 patients with endocardial fibroelastosis were the youngest; they died at a mean age of 2 months. Seven died at

Fig. 7. Retrograde aortogram. Filling of anterior right coronary from aorta. No filling of left coronary posteriorly. (Latter had origin from pulmonary artery.)

5 months or less; one lived to the age of 4½ years and was intensively studied by catheterizations and angiocardiograms. The mean age at onset of failure was 5 weeks. The most characteristic feature was the electrocardiographic pattern; in 7 there were changes of the S-T segments and T waves. Two of them showed right and 2 left ventricular strain. Other congenital defects were frequently found. The clinical response to digitalis was poor.

Myocarditis was confirmed by postmortem examination in 2 patients. These presented at an older age (12 months; 17 months) and died almost immediately after admission.

In 2 instances the diagnosis of glycogen storage disease was established by postmortem examination. Cardiac failure occurred at 6 and 7½ months, with death at 8½ and 9 months, respectively. These infants were not distinguishable clinically or electrocardiographically from those with myocarditis. One of the infants had a brother with the same condition who died subsequently in another hospital.

The single instance of an anomalous coronary artery occurred in a Negro male infant who was followed from 9 months to 4⅓ years of age because of recurrent cardiac failure and chest pain. He had no cardiac murmur, but there were marked electrocardiographic changes indicative of left ventricular strain and coronary insufficiency. A retrograde aortogram confirmed the clinical suspicion of an anomalous left coronary artery arising from the pulmonary artery (Fig. 7). An attempt at surgical repair was unsuccessful. At necropsy there were severe fibrotic changes in the left ventricle in addition to the anomalous coronary artery.

There were 4 patients (item 12 f in Table III) with large hearts, very abnormal electrocardiograms, and no murmurs, who died but were not examined post mortem. Two of them died at 5 days and at 2 months of age, respectively, and were thought to have endocardial fibroelastosis. The other 2 died at 4 months and at 1 year of age, respectively, and might have had any one of the endomyocardial lesions. Table III gives more details.

A more optimistic outlook is possible for 13 patients presumed to have had myocarditis who are still living (item 12 a in Table III). These infants developed signs and symptoms of cardiac failure at a mean age of 14 months; their clinical diagnosis was based on a consistent absence of murmurs and the presence of cardiac enlargement, hepatomegaly, dyspnea, and striking electrocardiographic changes. Six of them had electrocardiographic evidence of left ventricular strain and 3 of right-sided strain; all had S-T and T wave changes. Catheterizations were performed in 2 of the infants. All were digitalized and one infant also received quinidine. These patients have been followed from 2 months to 7 years or a mean of 17 months. Most of them have some persistent cardiac enlargement. Twelve of the 13 have been rechecked in recent months, and 9 are improving gradually as judged by electrocardiographic patterns and by decreasing heart size.

SUMMARY AND CONCLUSIONS

Cardiac failure in an infant should be suspected clinically when there are severe dyspnea, tachycardia, an enlarged heart, and hepatomegaly with or without edema or cyanosis. Bronchiolitis and pneumonia must be considered in the differential diagnosis. Serial electrocardiographic studies aid in evaluating the condition of the myocardium, and roentgenograms of the chest provide information relative to the size and shape of the heart and to the vascularity of the lungs. Such definitive studies as cardiac catheterization, angiocardiograms, and retrograde aortograms can be performed in the infant age group. When the diagnosis is not evident on the basis of other data, these special studies should be carried out on all infants with cardiac failure as soon as it is controlled.

The measures for the treatment of congestive cardiac failure in infancy are listed. Except in fibroelastosis and in the later

stages of myocardial failure, digitalis is a valuable adjunct.

Of the 115 infants with cardiac failure, 41 are living, a case fatality rate of 64 per cent. Of the 74 who died, 86 per cent were studied post mortem.

Although the prognosis of infants with cardiac failure is grave, it seems clear that a progressively larger percentage of them can be salvaged by identification of the underlying lesion and by adequate treatment. This is notably true in respect to patent ductus arteriosus, coarctation of the aorta, paroxysmal supraventricular tachycardia, pulmonic stenosis, myocarditis, and severe anemia.

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Craniosynostosis involving the sagittal suture only: Guilt by association?

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DURING the last decade there has been an increasing tendency among physicians to equate the diagnosis of craniostenosis with a recommendation for craniectomy. Cases of craniosynostosis involving only the sagittal suture are predominant in the various studies reporting the results of craniectomy. It has been repeatedly stated, however, that the decision for surgical treatment is more difficult in the cases of isolated synostosis of the sagittal suture since some children with this anomaly remain symptom free. In the uncertainty as to whether surgical treatment is indicated for the reasons of preventing increased intracranial pressure and allowing normal growth of the brain, many have proclaimed craniectomy desirable for the cosmetic effect.

On the basis of data presented in this paper it is our opinion that infants with isolated synostosis of the sagittal suture have been given an overly poor prognosis (without intervention) and that in such cases the condition has been linked in the manner of "guilt by association" with the more ominous sequelae attributed to the less common but more severe forms of craniosynostosis. A recent report by Gordon[1] supports this view. We would seriously question the advisability of subjecting all infants with isolated synostosis of the sagittal suture to craniectomy for the sole intent of obtaining a better cosmetic effect. It may be considered in some isolated cases, such as that presented by Mullan.[2]

THE GENERAL PROBLEM OF CRANIOSYNOSTOSIS

Virchow[3] introduced the term "craniostenosis" in 1851 to describe certain skull changes resulting from premature synostosis of the cranial sutures. He observed that when premature fusion of two cranial bones occurs, normal growth is inhibited in a direction perpendicular to the obliterated line of suture and compensatory growth occurs in a direction parallel to the fused suture. Because he believed that such a deformed cranium obstructed growth of the brain, he coined the term "craniostenosis," implying a narrowed or strictured skull. This term led to the confusion that still seems to persist in differentiating the usual microcephalic infant from the infant with craniosynostosis.

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It was Grieg[4] who later emphasized that in all forms of craniosynostosis the primary defect is cranial and not cerebral, with cranial deformity being the chief characteristic.

The etiology of craniosynostosis is unknown although many hypotheses have been presented and are quite fully discussed in the writings of Grieg,[4] Park and Powers[5] and others. Although there are 37 cranial sutures,[6] 7 of which are inconstant,[7] apparently only the 4 long sutures (sagittal, coronal, lambdoidal, and squamosal) are of clinical significance in craniosynostosis. Involvement of the coronal and sagittal sutures, alone or combined, determines the type of skull deformity present in the majority of cases of craniosynostosis.

Faber and Towne[8] suggested a simple but satisfactory classification by which most varieties of craniosynostosis can be categorized: (1) isolated closure of the sagittal suture, (2) isolated closure of the coronal suture, and (3) mixed craniosynostoses (two or more sutures involved). Isolated craniosynostosis of the sagittal suture is the most common form. The skull is keel or boat shaped, typically long and narrow, and hence the condition is described as scaphocephaly. In isolated craniosynostosis of the coronal suture, the head is short in its anteroposterior diameter, broad in its transverse or biparietal diameter, usually increased in its vertical dimension, and descriptively termed "brachycephaly." In the mixed form of craniosynostosis there is premature fusion of two or more sutures which may involve all of the long sutures of the cranial vertex. However, the shape of the skull will depend on whether the sagittal or coronal suture is involved. If both, the shape usually tends to be primarily influenced by closure of the coronal suture and hence tends to be brachycephalic. When all sutures are involved, oxycephaly or "tower head" results. In this study we have made a separate group of the mixed type, Crouzon's craniofacial dysostosis, in which there are a distinctive dysostosis of the facial bones and a strong familial tendency.

If Virchow's[3] hypothesis that a "stenosed" skull fails to accommodate a normal growing brain is correct, then premature fusion of several sutures would logically be expected to produce an increased intracranial pressure or deformity of the skull or both directly proportional to the age at onset and to the extent of suture closure. It would follow that surgical intervention to prevent or relieve the intracranial pressure and to allow normal growth of the brain would be indicated.[8-10] Many methods and techniques for craniectomy have consequently been developed. It seems, however, that such operations should be based on a relatively dependable predictability that without treatment such increase in intracranial pressure and the secondary effects attributed to it will occur. Most of the literature dealing with cranio-

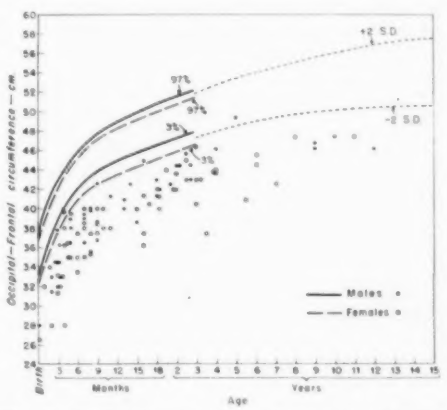

Fig. 1. Occipitofrontal circumference in 103 microcephalic infants and children.

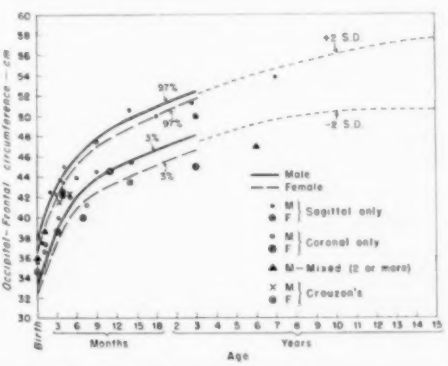

Fig. 2. Occipitofrontal circumference in 34 infants with craniosynostosis.

Table I. Clinical comparison of craniosynostosis and microcephaly

	Craniosynostosis		*Microcephaly*	
	No.	*%*	*No.*	*%*
Total cases	42		112	
Retardation	3*	7.1	112	100
Occipitofrontal circumference recorded	34		103	
<3rd percentile	4†	11.8	100	97.1
3rd percentile or more	30	88.2	3‡	2.9
Suture closure	42	100	9	8

*Borderline in 2 cases.

†Normal development in all.

‡Two patients had congenital toxoplasmosis; one was normal until acute meningitis at age 4 months. All had variable retardation.

synostosis has been primarily concerned with the problem of oxycephaly and its variations. These are the more severe types of craniosynostosis because of closure of multiple sutures and the predominant short, broad, and high skull. Craniosynostosis involving only the sagittal suture, although more common than the other forms, has not received so much attention.

The diagnosis of craniosynostosis should not be difficult. It is noteworthy that of the 42 cases of craniostenosis presented in this study the abnormally shaped skull was noticed at birth in 32 and at a later age in 10. This fact would suggest that fusion of the involved suture had begun during intrauterine life. Roentgenograms at this age (neonatal) may not show the typical sclerosing or peaking up described as being the diagnostic sign of premature fusion. It may be several months before there is positive roentgenographic evidence of fusion of the suture or sutures. Thus the shape of the head in the neonate may be of more diagnostic significance than the roentgenogram.

The differential diagnosis between craniosynostosis in a child with a normal brain and the microcephalic infant with an abnormal brain has long been somewhat of an enigma to many physicians. Approximately 40 years after Virchow's predicated theory of craniosynostosis, in the preroentgen era, the first surgical (craniectomy) procedures were developed. It is probable that Virchow's law led many to the assumption that patients with craniosynostosis ought to have a small head. The American surgeon, Lane,[11] in 1888, was approached by the mother of a 9-month-old "decidedly microcephalic imbecile" concerning whom she posed the question, "Can you not unlock my poor child's brain and let it grow?" Lane responded by doing one of the first craniectomies, and although this patient did not survive, a second microcephalic infant was operated upon, survived, and was reported by Lane to have given "unequivocal evidence of mental improvement." He further wrote: "Craniectomy is on trial, and though the surgeon's knife may 'unlock the brain,' it remains for futurity to determine how far his work will remove the penumbral shadow which microcephalus casts on infantile mentality."

Craniectomy in a microcephalic infant was reported by Lannelongue[12] in 1890 with optimism in regard to results. However, Jacobi,[13] proclaimed by many as the father of American pediatrics, took serious issue with such proclaimed successes and severely criticized such a procedure. In 1894, giving an address before the International Congress in Rome, he said: "Is it sufficient glory to don a white apron and swing a carbolized knife and is therein a sufficient indication to let daylight into a deformed cranium and on top of a hopelessly defective brain, and to proclaim a success because the victim consented not to die of the assault? No ocean of soap and water will cleanse those hands, no power of corrosive sublimate will disinfect the souls." So strong was Jacobi's persuasive and chastening argument that craniectomy was practically abandoned for almost 30 years. It is noteworthy, however,

that in the same address Jacobi had further observed that "if any cases be at all amenable to treatment by such an operation, they must be those of uncomplicated premature ossification of the sutures and fontanelles."

In conjunction with the study of craniosynostosis we reviewed the records and roentgenograms of 112 microcephalic infants and children seen at the Mayo Clinic during the period 1949 through 1958. A comparison of the occipitofrontal circumference of 103 of these infants with the occipitofrontal circumference of those with craniosynostosis is shown in Figs. 1 and 2. The basic differences in regard to retardation, occipitofrontal circumference, and closure of sutures are shown in Table I. Without exception the patients with microcephaly evidenced some unequivocal degree of mental retardation, with most being classified as imbeciles on the basis of psychometric tests. As noted in Table I, with very few exceptions the occipitofrontal circumference was well below the third percentile for age and sex. However, it was observed in these exceptions that some incident had occurred

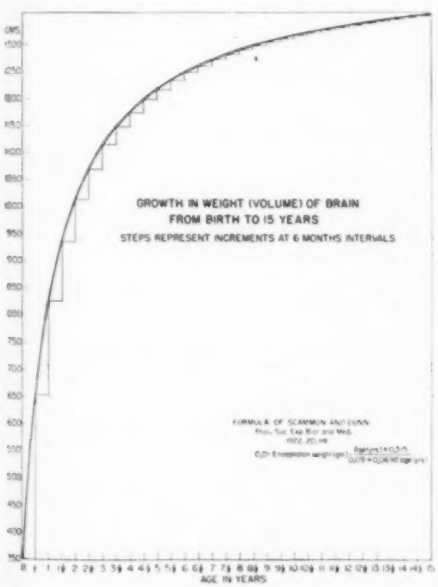

Fig. 3. Increase in weight of brain. (From Faber, H. K., and Towne, E. B.[10])

Fig. 4. Example of suboptimal craniectomy for craniosynostosis involving sagittal suture only. Appearance 5 years and 3 months after operation.

to arrest growth of the head after an initial period of normal growth. For example, one infant had been developing quite normally up to 4 months of age, when meningitis occurred. Although growth of the brain and head was subsequently retarded, the previously normal growth had the apparent effect of producing a relatively large head. Of further interest was infrequent roentgenographic evidence of premature closure of the sutures, although the ages ranged from birth to 35 years, and this in spite of the lack of normal growth-expansion stimulus. Roentgenographic evidence of fusion of one or more sutures was present in only 9 (8 per cent) of the 112 patients. This is not in agreement with the opinion expressed by Grieg[4] and by Simmons and Peyton,[14] who believed that with relative cessation of brain growth in microcephaly, a secondary premature synostosis commonly occurred. It is in harmony with Jacobi's[13] assertion that "in microcephaly, open sutures are the rule."

The problem of assessing skull capacity, present and predicted, and thus of deciding on surgical treatment to prevent the fettering of a normal brain in a skull of decreased capacity, is not as simple as one might surmise. Estimations of the true capacity of the skull based on measurements available in the living subject and comparison with norms

Table II. Details in 42 cases of craniosynostosis

Case	*Sex*	*Age of patient first seen*	*Age when deformity first noted*	*Suture*	*Principal symptoms*	*Developmental status**	*Family history**	*Seizures**	*Status anterior fontanel*	*Basic skull deformity*	*Circumference of head*		*EOM's strabismus*
											Cm	*Percentile**	
1	M	1 day	Birth	Sag.	Deformity only	N (normal)	0	0	1 cm.	Scaph.	35.5	50th	0
2	M	3 wk.	Birth	Sag.	Deformity only	N	0	0	2 cm.	Scaph.	37.5	75th	0
3	M	2 mo.	Birth	Sag.	Deformity only	N	0	0	2 cm.	Scaph.	42.5	90th	0
4	M	3 mo.	2½ mo.	Sag.	Deformity, font. small	N	0	0	Closed	Scaph.	42.3	90th	0
5	M	3½ mo.	Birth	Sag.	Deformity only	N	0	0	"Open"	Scaph.	43.7	97th	0
6	M	3½ mo.	Birth	Sag.	Deformity only	N	0	0	2 cm.	Scaph.	40.0	25th	0
7	M	4 mo.	Birth	Sag.	Deformity only	N	0	0	2 × 3 cm.	Scaph.	45.0	97th	0
8	F	4 mo.	Birth	Sag.	Deformity only	N	0	0	Closed	Scaph.	42.3	90th	0
9	F	4 mo.	Birth	Sag.	Deformity only	N	*9a*	0	??	Scaph.	42.5	90th	0
10	M	4 mo.	Birth	Sag.	Deformity, font. small	N	0	0	Closed	Scaph.	43.5	90th	0
11	M	6 mo.	Birth	Sag.	Deformity only	N	0	0	Closed	Scaph.	43.9	50th	0
12	M	9 mo.	Birth	Sag.	Deformity only	N	0	0	Closed	Scaph.	44.5	10th	0
13	M	14 mo.	Birth	Sag.	Deformity only	N	0	0	2 × 4 cm.	Scaph.	50.7	97th	0
14	M	18 mo.	16 mo.	Sag.	Deformity only	N	0	0	??	Scaph.	50.0	90th	0
15	M	33 mo.	Birth	Sag.	Deformity only	N	*15*	0	—	Scaph.	51.3	90th	0
16	F	3 yr.	Birth	Sag.	Deformity only	N *16*	0	0	—	Scaph.	50.0	75th	0
17	F	5 yr.	Birth	Sag.	Deformity only	N	*17*	0	—	Scaph.	??	??	0
18	M	7 yr.	Birth	Sag.	Deformity, face asymmetry	N	0	0	—	Scaph.	53.8	+2 S[illegible]a	0
19	M	6 wk.	Birth	Cor.	Deformity, prominent eyes	N	*19*	0	"Open"	Brachy.	36.5	50th	0
20	M	6 wk.	Birth	R. cor.	Asymmetry, prominent eyes	N	0	0	1 cm.	Plagio.	37.5	50th	0
21	F	3 mo.	Birth	L. cor.	Deformity only	N	*21a*	0	3 cm.	Plagio.	38.8	10th	Yes
22	M	5 mo.	Birth	Cor.	Deformity, cleft palate, syndactyly	N	0	0	"Open"	Brachy.	42.0	25th	0
23	F	7 mo.	??	Cor.	Deformity only	N	0	0	Closed	Brachy.	40.0	<3rd	0
24	M	7½ mo.	Birth	Cor.	Deformity only	N	0	0	??	Brachy.	41.3	<3rd	Yes
25	M	9 mo.	Birth	Cor.	Deformity, prominent eyes	N	0	0	??	Brachy.	47.5	97th	0

Perc...*	EOM† stra-bismus	Exoph-thalmos	Optic atrophy or papil-ledema*	Vision*	Intra-cranial pres-sure*†	Opera-tion*	Years observed	Mental status	Comment
50th	0	0	0	0	0	No *1*	1½	N (normal)	Scaphocephalic
75th	0	0	0	2	0	Yes	2	N	"Slight elongated head"
90th	0	0	0	0	0	Yes *3*	2½	N	"Head shaped up wonderfully"
90th	0	0	0	0	0	Yes	4½	N	Slight scaphocephaly
97th	0	0	0	0	0	Yes	4	N	Head elongated ("egg-shaped")
25th	0	0	0	0	0	Yes *6a, 6b*	1½	N	"Narrow, oval head only"
97th	0	0	0	0	0	No	4	N	"Active, alert, bright"
90th	0	0	*8a*	*8b*	*8a*	Yes *8c*	3½	N	Opacities improved: doing well
90th	0	0	0	0	0 *9b*	No	5¾	N	Normal child
90th	0	0	0	0	0	Yes *10*	6	N	I.Q. 108 at age 26 mo. head "a little narrower"
50th	0	0	0	0	0	No	3	N	"Slightly abnormal head"
10th	0	0	0	0	0	No	7	N	"Head longer only"
97th	0	0	0	0	0	No	2	N	"Better but head still long, narrow"
90th	0	0	0	0	0	No	No follow-up	—	——
90th	0	0	0	0	0	No	4½	N	Narrow head
75th	0	0	0	0	0	No	2	N	Normal child
??	0	0	0	0	0	No	2½	N	Normal active child
+2 SD *a*	0	0	0	0	0	No *18b*	5	N	"Slight asymmetry, excellent student"
50th	0	Yes	0	0	0	Yes	3	N	"Wide forehead with left-sided asymmetry"
50th	0	Yes	Yes	0	Yes	Yes	1½	N	Slight residual papilledema (last seen 1958)
10th	Yes	0	*21b*	0	*21b*	Yes *21c*	3¼	N	Slight strabismus, hyperopia, forehead recessed
25th	0	Yes	Yes	?	Yes	No	No follow-up	—	——
<3rd	0	0	0	0	0	No	No follow-up	—	Did not return for advised operation
<3rd	Yes	0	0	0	0	Yes	3	Borderline	Walked at 2 yr.; slow talker; head shape improved, still brachy.
97th	0	Yes	Yes	0	Yes	No	12	N	Badly shaped head but improved; L. eye removed at 3½ yr. (proptosis); general health good

Table II. Cont'd

Case	*Sex*	*Age of patient first seen*	*Age when deformity first noted*	*Suture*	*Principal symptoms*	*Developmental status**	*Family history**	*Seizures**	*Status anterior fontanel*	*Basic skull deformity*	*Circumference of head*		*EOM stra-bismu*
											Cm.	*Percentile**	
26	F	11 mo.	Birth	Cor.	Deformity only	N	0	0	4 cm.	Brachy.	44.5	10th	0
27	M	14 mo.	??	Cor.	Deformity, prominent eyes	N	*27*	0	Closed	Brachy.	45.5	10th	Yes
28	F	3 yr.	Birth	Cor.	Deformity, prominent eyes	N	*28*	0	—	Brachy.	45.0	<3rd	Yes
29	F	5 yr.	3½ yr.	Cor.	EOM† imbalance	N	0	0	—	Brachy.	??	—	Yes
30	M	35 yr.	Birth	Cor.	Deformity, headache	N	0	0	—	Brachy.	??	—	0
31	M	5 wk.	Birth	Sag., cor.	Deformity, prominent eyes	N	0	0	??	Oxyceph.	36 (at birth)	75th	0
32	M	5 wk.	Birth	Sag., R. cor.	Deformity only	N	0	0	??	Scaph.-plagio.	38.7	90th	0
33	M	6 mo.	Birth	Cor.	Deformity, syndactyly	N	0	0	"Open"	Oxyceph.	??	—	0
34	M	14 mo.	Birth	Sag., cor.	Deformity only	N *34*	0	0	Closed	Scaph.	??	—	0
35	M	6 yr.	4 yr.?	Sag., cor., lambd.	Deformity, headaches, exoph., blindness	N	0	0	—	Oxyceph.	47.0	3rd	0
36	M	27 yr.	2 yr.?	Sag., cor., lambd., squam.	Blindness	N *36*	0	0	—	Oxyceph.	??	—	0
37	F	1 day	Birth	Cor.	Crouzon's; syndactyly	N	0	0	"4 FB"	Crouzon's	34.5	50th	0
38	M	3½ mo.	Birth	Cor.	Deformity, syndactyly	N	0	0	4 × 6 cm.	Crouzon's	41.5	75th	0
39	M	5 mo.	??	Cor., lambd.	Poor head growth	Abn.	0	*39*	3 × 8 cm.	Crouzon's	42.0	25th	Yes
40	F	14 mo.	Birth	Sag., cor., lambd.	Prominent eyes and jaw	N	0	0	"3 FB"	Crouzon's	43.5	<3rd	0
41	F	5 yr.	3 yr.?	Sag., cor.	Prom. eyes, poor vision, headache	N	*41*	0	—	Crouzon's	??	—	Yes
42	M	11 yr.	6 mo.	Sag., cor., lambd.	Prom. eyes, poor vision	N	*42*	0	—	Crouzon's	??	—	Yes

*Italicized numbers in this column refer to footnotes.

†As judged by clinical symptoms, funduscopic evidence of papilledema or optic atrophy, or roentgenologic evidence (suture separ... or pneumoencephalographic findings), or combinations of these manifestations. (EOM = external ocular movements.) *1.* Laryngo... transient cardiac arrest at time of proposed operation. *2.* Retinal, preretinal hemorrhages (fundus); discs normal; subdur... negativ... Suboptimal craniectomy. *6a.* Suboptimal craniectomy. *6b.* Three to four apneic spells, cyanosis postoperatively. *8a.* Equivo... al mild p... of discs. *8b.* Corneal opacities (congenital). *8c.* Suboptimal craniectomy. *9a.* Two older siblings with similar deformity at birth (aut... matic, normal). *9b.* Normal pneumoencephalogram. *10.* Suboptimal craniectomy. *15.* Maternal uncle, cousin, have "long narrow h...

* to that o... to percentil... by "looks ... eratively. ...te. *39.* Se... with simila...

	EOM† strabismus	Exophthalmos	Optic atrophy or papilledema*	Vision*	Intracranial pressure*†	Operation*	Years observed	Mental status	Comment
	0	0	0	0	0	Yes	11	N	Strabismus; head "about same"
	Yes	Yes	Yes	Blind	Yes	No	11	N	On honor roll (school for blind)
	Yes	0	0	0	0	Yes	1	N	"Doing well"
	Yes	0	0	0	0	No	No follow-up	—	——
	0	0	0	0	0	No	No follow-up	—	——
	0	Yes	0	0	0	No	3¾	N	At age 4 yr. normal save proptosis, deformity
	0	0	0	0	?	Yes	10 mo.	N	Good head growth, normal development, strabismus
	0	0	0	0	0	No	No follow-up	—	——
	0	0	0	0	0	Yes	4½	N	I.Q. 100, speech slow; otherwise fine
	0	Yes	Yes	Blind	Yes	Yes	3½	N	R. eye blind; L. 20/20. Normal otherwise
	0	Yes	Yes	Blind	Yes	No	No follow-up	—	——
	0	Yes	0	0	Yes	Yes	8 mo.	?	Developmental status equivocal
	0	Yes	0	0	?	Yes	3¼	N	Head "high but rounded out with age"
	Yes	Yes	Yes	?	Yes	Yes	2	Slow	Died at age 2½ yr.; seizure day of death; necropsy (inc. brain) neg.
	0	Yes	0	0	0	Yes	6½	N	"Bright," I.Q. 113
	Yes	Yes	Yes	Yes	Yes	No	No follow-up	—	Operation advised; refused
	Yes	Yes	Yes	Yes	Yes	Yes	4	N	Vision slightly improved; "B's" and "C's" at school

to that of patient. *16.* I.Q. 138. *17.* Maternal aunt with similarly shaped head. *18a.* Standard deviation utilized for reason of percentile tables for this age). *18b.* Operated on elsewhere at 17 months of age; roentgenograms indicate suboptimal craniectomy. by "looks like mother" (head shape). *21a.* Sister of Patient 28. *21b.* Fundi normal on admission; equivocal mild papilledema 2 years eratively. *21c.* Suboptimal craniectomy. *27.* Brother of Patient 22. *28.* Mother has hypertelorism. *34.* I.Q. 96. *36.* University te. *39.* Seizure on day of death only. *41.* Six relatives with similar deformities of face and head (four generations). *42.* Six relawith similar deformities of face and head (three generations).

are not available. Correlations between the size of the skull, the weight of the brain, and normal development are well recognized. Coppoletta and Wolbach[15] and Scammon and Dunn[16] showed that the weight of the brain increases about 85 per cent in the first 6 months and 135 per cent in the first year, and that by approximately 3 years of age the brain has reached 80 per cent of its adult volume. These relationships, shown graphically in Fig. 3, were based on empirical formulas derived from actual weight of the brain as observed in 2,956 individuals who had no cerebral lesions. Among normal persons of all races the capacity or volume of the cranial cavity that has been used in calculating the size of the brain is given as between 1,000 and 1,800 c.c., with an average of 1,400 c.c. On this basis anatomists define microcephaly as a condition in which the cranial cavity has a capacity of less than 1,300 c.c.; mesocephaly as one in which the capacity is 1,350 to 1,450 c.c.; and megacephaly as one in which the capacity is greater than 1,450 c.c. Despite this knowledge of norms of brain size and cranial capacity, the problem in a particular patient with craniosynostosis is whether the skull (deformed as it may be by prematurely fused sutures) is accommodating the normal growing brain. It has not been shown that distortion of the brain per se causes cerebral malfunction. As mentioned above, such a measurement is not available in the living subject.

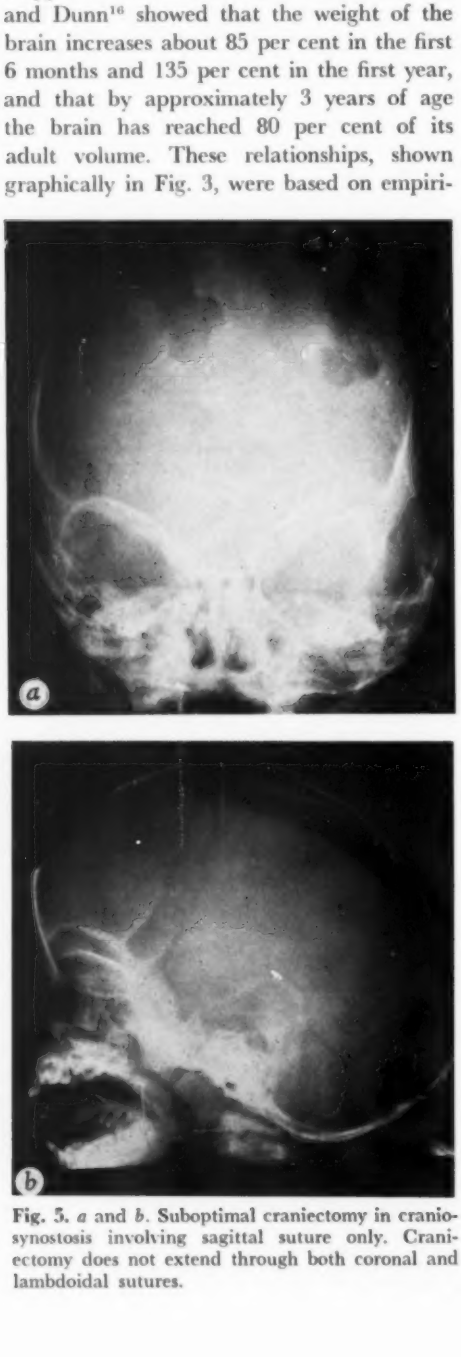

Fig. 5. *a* and *b*. Suboptimal craniectomy in craniosynostosis involving sagittal suture only. Craniectomy does not extend through both coronal and lambdoidal sutures.

From the clinical standpoint, however, the occipitofrontal circumference offers one practical measurement in estimating brain growth and intracranial volume. Norms for circumference of the head based on a normal-curve distribution or percentiles or both are available for reference. At the same time it must be recognized, as stated by Watson and Lowrey,[17] that in abnormally shaped heads (craniosynostosis) the usual occipitofrontal circumference does not indicate the true volume of the cranial vault. As will be shown later, the occipitofrontal circumference in the scaphocephalic skull tends to be above average as compared with standards for children with normally shaped heads. The appearance of the scaphocephalic skull and the tendency to above-average occipitofrontal circumference are somewhat of a geometric illusion and do not prove that the cranial volume is correspondingly above average or even comparable. Conversely, in the brachycephalic patient the appearance and the occipitofrontal circumference suggest that the size of the skull, and therefore the cranial volume, is less than average. This

Table III. Summary of 42 cases of craniosynostosis

Group	Cases	Sex		Age deformity noted				Positive family history	History of seizures	Increased intracranial pressure*	Exophthalmos	Optic atrophy, papilledema	Developmental status	
		M	F	Birth	1 yr.	After 1 yr.	Unknown						Normal	Retarded
Sagittal (only)	18	13	5	16	1	1	0	3	0	0†	0	0†	18	0
Coronal (only)	12	7	5	9	2	1	0	4	0	5‡	5	5‡	11	1§
Mixed (2 or more)	6	6	0	4	0	2	0	0	0	3‡	3	2	6	0
Crouzon's disease	6	3	3	3	2	0	1	2	1‖	5‡	6	3	4	2¶
Total	42	29	13	32	5	4	1	7	1	13	14	10	39	3

*Increased intracranial pressure as judged by clinical symptoms, funduscopic evidence of papilledema or optic atrophy, or roentgenologic evidence (separation of sutures or pneumoencephalographic findings), or combinations of these manifestations.

†Equivocal papilledema in one case.

‡Equivocal in one case.

§Borderline retardation.

‖Seizure on day of death only.

¶One borderline retardation.

also is a geometric illusion since the vertical dimension in brachycephaly is increased and the shape of the head is more that of a sphere.

If craniectomy is proposed to relieve or prevent intracranial pressure resulting from reduced capacity of the skull, the evidence that such increased pressure actually exists or may reasonably be expected to develop should be quite definite. There is not general agreement that such evidence is present or predictable. This appears to be especially true for craniosynostosis involving the sagittal suture only. Grieg,[4] Park and Powers,[5] and others have discussed the changes in the cranial fossae in the mixed type of craniosynostosis. They have particularly described the shortening and heightening of the anterior fossa with the resultant effect on the orbits and the frequently associated strabismus, exophthalmos, papilledema with or without optic atrophy, and blindness.

Optic atrophy developed in 67 (91 per cent) of 74 cases of oxycephaly included in Günther's[18] tabulation. Such sequelae have commonly been attributed to a general increase in intracranial pressure. Grieg,[4] however, believed that the visual disturbances are due to a variety of factors, namely: (1) small optic foramen, (2) increased intracranial pressure, (3) upward deflection of the optic nerve with displacement secondary to the deformed anterior and middle cranial fossae, and (4) defective arterial blood supply and restriction of venous return. It was his contention that increased intracranial pressure alone did not explain the optic neuritis seen so commonly in oxycephaly.

On the other hand, if therapy for craniosynostosis is to be undertaken as a preventive measure, it has seemed logical to suggest that it be done prior to the period of rapid growth of the brain. As emphasized by Grieg,[4] craniosynostosis developing concurrently with or after cessation of brain growth has no clinical significance. This fact was well brought out in Bolk's[19] study of 1,820 skulls representing ages from 3 to 20 years as determined by dental formulas. Bolk found a total of 343 skulls, or 19 per cent, in which one or more sutures were obliterated. Previously most anatomists had said that the cranial sutures seldom normally fused before the third decade of life and that such closure might not occur until as late as the eighth decade. He observed that the frequency of premature closure was essentially the same for the age level 3 to 7

years as it was for the age level 13 to 20 years. He believed that in so far as the sagittal suture was concerned the number of skulls with premature obliteration and without any sign of scaphocephaly was "too large to accept the point of view that such an individual died shortly after synostosis and that therefore the skull had no time to deform."

PRESENT STUDY

The present study was initiated when one of us (L. E. H.), because of past experience in following a number of normally developing children who had scaphocephaly, questioned the indications and advisability of subjecting a particular infant to craniectomy for premature closure of the sagittal suture only. Further stimulus was given when laryngospasm occurred with cardiac arrest of about 20 seconds during the course of induction of anesthesia in this infant for the proposed operation. The infant revived and the operation was deferred. Subsequently the growth and development of this infant to the present age (1½ years) have been normal.

Although the major concern in this study is with the patients who have craniosynostosis that involves the sagittal suture only, all of the cases of craniosynostosis encountered at the Mayo Clinic in the 25 year period from Jan. 1, 1934, through Dec. 31, 1958, were reviewed. There were 42 cases of craniosynostosis, and these have been divided into four groups: (1) craniosynostosis involving the sagittal suture only (18 cases), (2) craniosynostosis involving the coronal suture only (12 cases), (3) craniosynostosis involving two or more sutures—mixed (6 cases), and (4) craniosynostosis of Crouzon's type (craniofacial dysostosis) (6 cases). The data for the entire series are presented in Table II. Follow-up was either by examination or by personal letter seeking to assess developmental status, ophthalmologic changes, the presence of seizures, and the degree of handicap attributable to the cosmetic deformity.

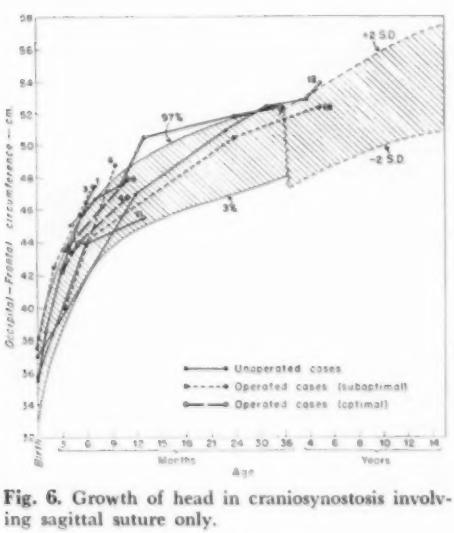

Fig. 6. Growth of head in craniosynostosis involving sagittal suture only.

Craniosynostosis involving sagittal suture only. There were 18 cases of isolated craniosynostosis of the sagittal suture. The presenting complaint or the reason for referral to the clinic was the "deformity" of the head in all 18 cases. The unusual shape of the head had been noted at birth in 16 cases, suggesting that fusion of the suture had occurred before birth in these infants. Ten of the 18 children had no surgical procedure. Eight were operated upon, but 4 of these were assessed as having had suboptimal craniectomy. We have used the term "suboptimal" because in 2 cases the type of procedure done (example: Fig. 4) could not be expected either to relieve pressure or to allow normal growth of the head, and in the other 2 cases, in which the intent was apparently to do a craniectomy in the manner described by Ingraham and associates,[20] the craniectomy was not extended through both the coronal and sagittal sutures (example: Fig. 5).

No child with craniosynostosis involving only the sagittal suture evidenced retardation at the time of the initial examination, and retardation had not become evident in any of the 17 on whom follow-up information was obtained.

Neither headache in children old enough to localize such a complaint nor irritability

suggesting discomfort was present in any of the 18. In the infants whose anterior fontanel was still open there was no bulging. None showed exophthalmos or strabismus. Seventeen had normal funduscopic findings with no evidence of papilledema or optic atrophy, and in so far as it was determined vision was normal. In one case corneal opacities had been present since birth; when the infant was seen at the age of 4 months because of the scaphocephaly, the left fundus could not be visualized. The right disc was thought to show either glial proliferation or possible chronic papilledema. This child had a suboptimal craniectomy at that time (age 4 months). When last examined at the age of 3½ years the corneal opacities were less dense and the right disc was noted to be flat though somewhat distorted and showed no evidence of papilledema. The left disc still could not be visualized. Vision in the right eye was apparently normal. Growth and development were normal.

In none was there roentgenographic evidence of separation of the nonfused sutures. Thus in none of the 18 cases of craniosynostosis involving the sagittal suture was there convincing evidence of increased intracranial pressure.

It is of further interest, as graphically demonstrated in Fig. 6, that the heads of those who did not have surgical treatment showed the same gradual progressive enlargement anticipated for age and sex as did those who did have surgical treatment. Four of the children shown in this figure had no operation and 5 had craniectomy. In 3 of the 5 who had craniectomy, the operation was considered suboptimal. It should also be noted that in the follow-up there is at least a question raised as to whether surgical treatment greatly affected the shape of the head.

Craniosynostosis involving coronal suture only, craniosynostosis involving two or more sutures, and Crouzon's disease. A comparative summary as to age when deformity of the skull was first noticed, developmental status, ophthalmologic findings, and miscellaneous clinical features is given in Table III

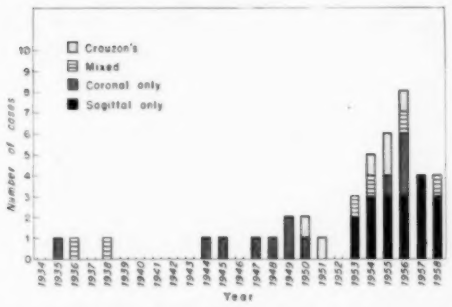

Fig. 7. Distribution of 42 patients with craniosynostosis according to year first examined at the Mayo Clinic.

for all four groups of cases, inclusive of the three groups just mentioned. Five of the 6 cases of Crouzon's disease have been reported previously.[21]

COMMENT

Inasmuch as 15 of the 18 patients with craniosynostosis involving the sagittal suture alone had either no surgical treatment (10 patients) or surgical treatment that could not be expected either to increase the cranial volume or to prevent stenosis (5 patients), it seems logical to question the unqualified recommendation for craniectomy at an early age as a preventive measure in these patients. The desirability of craniectomy in the more serious type of craniosynostosis is not questioned at this time but may require closer scrutiny in selection of cases, type of surgical procedure, and evaluation of results.

In consideration as to whether craniectomy in the scaphocephalic child should be done for purely cosmetic reasons, one must recognize that definite morbidity and mortality are associated with anesthesia and surgical treatment of this magnitude in the small infant. Although there were no operative deaths in our rather limited number of surgical cases, one infant experienced cardiac arrest during induction of anesthesia and a second (with suboptimal craniectomy) experienced four episodes of severe apnea and cyanosis postoperatively. In one series[22, 23] of 29 infants with craniosynostosis, 22 had craniectomy; there was one death

from surgical shock, that of one of 9 patients who underwent operation for involvement of the sagittal suture only. Although no doubt the mortality rate is low in the hands of the neurosurgeon who has had wide experience in the technique of this type of craniectomy, there are few published reports of the outcome in smaller series of craniectomies in many of the medical centers. Furthermore, the degree of cosmetic improvement after adequate craniectomy may be open to question. In the 3 infants who had adequate craniectomy in our series, scaphocephaly persisted in varying degrees. Further, in one case in which suboptimal craniectomy had been done, the parents reported that "his head has shaped up wonderfully well" although critical review of photographs before operation and subsequently hardly allows one to be enthusiastic about the supposed change in the shape of the head.

Fig. 7 shows the distribution of the 42 cases of craniosynostosis according to year seen at the Mayo Clinic. Although the study represented a period of 25 years (1934 through 1958), all of the cases of craniosynostosis involving the sagittal suture alone were encountered after 1952. As stated previously, approximately 112 children with retardation and microcephaly were seen in the 10 year period 1949 through 1958, and these were but a portion of the number seen primarily because of retardation. This alone would suggest that craniosynostosis involving only the sagittal suture rarely causes retardation. It probably also reflects the resurgence of interest in advocating surgical treatment in craniosynostosis and, as pointed out before, the tendency to equate the diagnosis of craniosynostosis of any type with a recommendation for surgical treatment.

SUMMARY

The clinical findings in 42 cases of craniosynostosis are summarized. Eighteen patients had craniosynostosis involving only the sagittal suture. Ten of the 18 did not have surgical treatment, while 5 had inadequate and 3 had adequate surgical procedures. We believe that patients with craniosynostosis involving the sagittal suture alone have been given an unwarrantedly poor prognosis in regard to development, and we question advocation of craniectomy for cosmetic reasons alone.

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Congenital abnormalities of the urinary system

I. A postmortem survey of developmental anomalies and acquired congenital lesions in a children's hospital

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ANOMALIES of the genitourinary tract occur in approximately 10 per cent of the population and account for a third of all congenital malformations.[1, 2] The incidence, classification, and morphology of urinary tract anomalies have been the subjects of extensive studies.[2-6] Detailed histologic investigations of renal malformations have provided information about their morphogenesis[7, 8]; cystic conditions, in particular, have been studied by serial reconstruction[9] and microdissection.[10]

As an initial step in studying congenital abnormalities of the urinary tract and their morphogenesis we have undertaken a survey of postmortem material at Children's Hospital of Michigan. Particular attention has been directed toward patterns of malformation in an attempt to delineate the effect of one abnormal part on other components of the system and to separate developmental anomalies from secondarily acquired lesions.

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SELECTION OF MATERIAL

The present study is based upon 180 cases of congenital urinary tract abnormalities occurring in 2,153 consecutive autopsies of infants and children up to 12 years of age performed during the 10 year period, 1950 to 1959. The percentage of newborn infants is proportionately low, because the hospital has no obstetric service, but 90 per cent of the autopsies have been on infants in the first year of life. This survey has been oriented primarily toward abnormalities of the kidney; other abnormalities have been correlated with them as a frame of reference. Malformations capable of causing malfunction or leading to clinical symptoms were considered to be significant. Glomerulonephritis and the nephrotic syndrome occurring in the first 6 months of life, pyelonephritis in the first 3 months, and hemorrhagic or ischemic necrosis in the first few days have also been included in order to evaluate the role of maldevelopment in the pathogenesis of "congenital" nephritis.

Renal abnormalities have been evaluated in relation to abnormalities of the lower urinary tract and to malformations of other organ systems. Finally, several clinical categories of congenital urinary tract disease in

addition to the so-called congenital nephritides, have been evaluated with respect to specific anatomic urinary tract malformations.

CLASSIFICATION OF RENAL ABNORMALITIES

Anomalies of structure.

Agenesis. This has been defined as the absence of identifiable renal tissue. The 11 cases included 2 that were bilateral and 9 that were unilateral (Table I). Four of the 9 children with unilateral agenesis died in renal insufficiency; one had hypoplasia and another dysplasia of the other kidney, and 2 had dilated ureters and pyelonephritis. The 2 cases of bilateral agenesis were remarkable for having had none of the anomalies described by Potter,[4, 11] such as abnormal facies and hypoplastic lungs. In one case of unilateral agenesis the ear on the same side as the absent kidney was malformed, and one other infant with unilateral agenesis had bilaterally hypoplastic lungs.

Hypoplasia. Hypoplasia has been defined as a congenitally decreased amount of histologically normal renal tissue. Two subcategories have been recognized: (1) simple hypoplasia in which there is a deficiency by weight of otherwise normal renal parenchyma; and (2) dysplastic hypoplasia, in which there are structures within the kidney suggestive of embryonic maldevelopment.

SIMPLE HYPOPLASIA. When one kidney weighed 50 per cent or less than expected[4, 12] and the contralateral kidney approximated normal size, it was regarded as unilateral hypoplasia. When each kidney weighed less than expected, a reduction in weight of one third or more in the combined renal mass was regarded as bilateral hypoplasia.

Of 58 cases of simple hypoplasia, only 2 were unilateral. In one instance there was only one kidney which was only three fourths the expected size; this case was arbitrarily listed as unilateral hypoplasia.

The bilateral cases were subdivided into two groups: 16 with severe hypoplasia, with less than one half the expected combined renal mass, and 39 with moderate hypoplasia, with one half to two thirds the expected renal mass. These cases were, as a group, not associated with other genitourinary anomalies (Table I). Anomalies of other systems, on the other hand, were common, occurring in 32 of the 58 cases (Table II). Cardiovascular malformations were present in 14, and there were anomalies of the alimentary tract in 10 instances, in 8 of which there was some form of congenital stenosis or atresia.

DYSPLASTIC HYPOPLASIA. The criteria for dysplasia were similar to those elaborated by Marshall[7] and by Ericsson and Ivemark.[8] Malformed structures included: (1) large primitive ducts, which were lined by poorly differentiated columnar or transitional epithelium, surrounded by fibromuscular collars or concentric rings of fibrous tissue, and which were generally found in the medulla; (2) small primitive ductules, which were lined by undifferentiated epithelium and which were generally located in the cortex; (3) heterotopic nests of cartilage; and (4) cortical or medullary cysts, which were lined by actively growing, undifferentiated epithelium.

Dysplastic hypoplasia was classified in four anatomic subgroups: (1) multicystic dysplasia, in which cysts of varying sizes surrounded a central core of disorganized but identifiable renal tissue, and with which there was customarily an associated ureteral atresia; (2) medullary dysplasia, in which the collecting ducts were primitive and diminished in number, and in which the medullary pyramids were malformed and contained an abundance of fibrous or fibromuscular tissue; (3) cortical dysplasia, in which the periphery of the cortex contained poorly differentiated and sclerotic renal elements, frequently in association with subcapsular cysts; and (4) corticomedullary dysplasia, in which the features of the second and third groups were combined, and in some of which the hypoplasia was so extreme and associated with such marked disorganization that it would be considered as "aplasia" in some classifications.

Table I. The association of primary renal malformations with other urinary tract anomalies

Primary renal anomalies	Total No. of cases	Associated urinary tract anomalies																	No associated urinary tract anomaly
		Kidney							Ureter						Bladder and urethra					
		Agenesis	Simple hypoplasia	Dysplastic hypoplasia	Ectopia	Duplication	Fusion	None	Atresia	Stenosis	Megaureter	Duplication	Ureterocele/ectopia	None	Exstrophy	Megacystis	Posterior urethral valve	Other urethral obstruction	None	
A. Anomalies of structure																				
1. Agenesis																				
Bilateral	2	×						2						2					2	2*
Unilateral	9	×	1†	1†	1†			6†	1†	1†	2†			5†					9	3*
2. Hypoplasia																				
a. Simple																				
Bilateral	55		×		3		1	52			2		1	52		1			54	50
Unilateral	3	1†	×					2						3			1		2	1
b. Dysplastic																				
Bilateral	16			×	1			15	3	1	2			10		1	8	2	5	2
Unilateral	15	1†		×	2		1	12	7	2	1		3	2	1		1		13	1
3. Polycystic disease	3							3						3					3	3
B. Anomalies of position and shape																				
1. Ectopia																				
a. Simple unilateral	10	1†	2	2	×			5	2	1			1	6					10	4
b. Crossed	6			1	×		6	0			1		1	3					6	0
c. Bilateral	15		1		×		15	0				3	1	12				1	14	0
2. Duplication	14				3	×	3	11			1	14		0					14	0

*The ureter on the affected side was totally missing in all but one case of renal agenesis.

†These figures refer to the contralateral kidney and ureter.

Fifteen of the cases of dysplasia were unilateral, and 13 of these had ureteral anomalies (Table I). Seven of the atretic ureters were associated with the multicystic variety of dysplasia; the latter was seen only in association with ureteral atresia. Of the 16 bilateral cases, 10 had lower urinary tract obstruction in the form of a valve or atresia of the posterior urethra and one other had megacystis, which can be regarded as presumptive evidence of infravesical obstruction. Two others had bilateral ureteral obstructive abnormalities, but in two there was no evidence of urinary tract obstruction. Anomalies of other systems were less common than in association with simple hypoplasia (Table II); of these 7 of 9 cardiovascular anomalies were aortic coarctation and 5 of 7 alimentary tract anomalies were imperforate anus.

Polycystic disease. This has been defined as a marked degree of diffuse, though not necessarily uniform, tubular and/or glomerular dilatation characterized by enlargement of the kidneys and occasionally by gross cyst formation. Only 3 cases, each with additional polycystic changes in the liver and pancreas, were recognized; none of them had other malformation of the urinary tract.

Anomalies of position and shape.

Ectopia. The abnormal location of one or both kidneys was encountered in unilateral, crossed, and bilateral forms. The "horseshoe" kidney has been classified as a fused form of bilateral ectopia. Major renal anomalies were present in 5 of 10 cases of simple ectopia, and ureteral anomalies were frequently encountered with each of the three forms (Table I). Ectopia seemed to occur as one of multiple malformations; 26 of the 31 cases were associated with anomalies of other organ systems (Table II).

Duplication. The demonstration of more than one collecting system in either kidney, with or without overt evidence of duplication of the renal mass, was called duplication. A double ureter was taken as prima facie evidence of renal duplication. Of the 14 cases, 6 were bilateral and 8 unilateral (Table I). Malformations of other systems were commonly present (Table II).

Congenital nephritis. The 5 cases of *glomerulonephritis* (Table III), including 3 with the nephrotic syndrome, were not associated with other genitourinary malformations. All had been diagnosed during the first 6 months of life. The clinical diagnosis of *pyelonephritis* was confirmed at autopsy in 20 infants under 3 months of age. None of the 9 in whom the lesion was acute had gross or microscopic evidence of urinary tract malformation. Of the remaining 11 with chronic pyelonephritis, all had some form of urinary tract malformation (Table III).

Ischemic necrosis, either cortical or medullary, was present in 5 infants who died during the first week of life. One infant lived for a month and died with a healing lesion, but hematuria had been present from the day of birth. These lesions were notable in that there were no associated malformations. None of the infants developed hypertension. One had sufficiently severe anemia to produce shock, and 3 had low hemoglobin values on the first day of life. Areas of ischemic necrosis were frequently present in the livers, adrenals, and brains of these infants, and all appeared to have suffered from anoxia and shock.

ABNORMALITIES OF THE LOWER URINARY TRACT

Exstrophy of the bladder, the megacystis-megaureter syndrome, vesical outlet obstruction, and deficiency of abdominal musculature were selected as malformations that might be encountered in clinical practice. These cases, which numbered 30, were tabulated to clarify any pattern of associated renal malformation that might emerge (Table III).

The single case of bladder exstrophy was associated with unilateral renal dysplasia and ureteral atresia. Dilated and hypertrophied bladders and ureters without a demonstrable bladder neck or urethral obstruction, that is the megacystis-megaureter syndrome, were encountered 8 times. Only one of these children had Hirschsprung's

Table II. The association of primary renal anomalies with malformations of other systems

Primary renal anomalies	*Total No. of cases*	*Associated*														
		Cardiovascular							*Alimentary tract*							*Respira*
		Ventricular septal defects	*Atrial septal defects*	*Valvular anomalies*	*Transposition of great vessels*	*Preductal aortic coarctation*	*Other (patent ductus arteriosus, vascular rings, etc.)*	*Total with cardiovascular anomalies*	*Malrotation*	*Tracheoesophageal fistula*	*Imperforate anus*	*Other intestinal atresia and stenosis*	*Polycystic liver and pancreas*	*Aganglionosis*	*Total with gastrointestinal anomalies*	*Abnormal lobation*	*Pulmonary hypoplasia*
I. Anomalies of structure.																	
A. Agenesis																	
1. Bilateral	2							0	1						1		
2. Unilateral	9				1		1	1	1	2	1				4	1	1
B. Hypoplasia																	
1. Simple	58	6	3	2	3	1	10	14	3		4	6			10	2	1
2. Dysplastic	31	3	3		1	7	3	9	1	2	5	1			7	5	
C. Polycystic disease	3							0					3		3		
II. Anomalies of position and shape.																	
A. Ectopia																	
1. Simple unilateral	10	2					1	3		2	2				4	3	1
2. Crossed unilateral	6	3			1	1	1	3	1						1		
3. Bilateral	15	8			2	3	2	10		4					4	2	
B. Duplication	14	3	2	2		2	2	8	1	1	1	1			4	2	

disease. Posterior urethral valves were found in 18 infants, half of whom had renal dysplasia; none had any other urinary tract malformation aside from occasional cystic remnants at the apex of the bladder. Dysplastic renal hypoplasia was present in each of 2 infants who had urethral atresia and one who had posterior urethral stenosis.

Deficiency or hypoplasia of the abdominal musculature was associated with lower urinary tract obstruction in each of 4 infants: 2 had the megacystis-megaureter syndrome, one had a posterior urethral valve, and one had posterior urethral stenosis.

ANOMALIES OF OTHER SYSTEMS

The 148 primary renal malformations that have been described occurred in 136 infants, of whom 99 (an incidence of 72.8 per cent) also had malformations of other organ systems (Table II). Principal among these were cardiovascular anomalies which occurred in 42, an incidence of 31 per cent; in the entire autopsy series of 2,153 cases there were 410 malformations of the cardiovascular system, an incidence of 19 per cent. There were also 24 cases of tracheoesophageal fistula, intestinal atresia or stenosis, and imperforate anus, an incidence of approximately 18 per cent, compared with 5 per cent (106 cases) in the entire autopsy series.

Interventricular septal defect was the most common cardiac anomaly, occurring 21 times. Among 58 infants who had simple renal hypoplasia there were 14 cardiovascular malformations, including 6 interventricular septal defects and only one aortic coarctation. Among the 31 cases of dysplastic hypoplasia, on the other hand, there were 7

Total with gastrointestinal anomalies	anomalies																								
	Respiratory			Central nervous					Genitourinary					Musculoskeletal											
	Abnormal lobation	Pulmonary hypoplasia	Total with pulmonary anomalies	Opacities and anomalies of eye	Hypoplasia	Arnold-Chiari malformation	Aqueductal atresia	Total with central nervous system anomalies	Phallic abnormalities	Uterovaginal duplication	Uterovaginal hypoplasia	Pseudohermaphroditism	Total with genital anomalies	Abnormal facies	Cleft palate/harelip	Talipes	Hernia	Abdominal muscle deficiency	Osseous deformities	Total with musculoskeletal anomalies	Total with no anomalies
1			0					0					0							0	1
4	1	1	1		1			1	1		1		2	1			1			2	3
10	2	1	3	1	5	3	1	10	1	2	2		5	2	3	3	1		4	10	26
7	5		5		2			2	2	1	2	1	3	2	1	1	1	1		6	16
3			0					0					0							0	0
4	3	1	4	1	2			2					0	1						1	2
1			0	1	1	1		2					0		1		1		2	2	1
4	2		2	2	2	1		4					0	4	4	3	2		4	9	2
4	2		2	1	1			9	1				10	3	3	3	1		3	7	0

instances of aortic coarctation. Renal positional abnormalities were also associated with cardiovascular anomalies.

Alimentary tract abnormalities were found in 34 infants, 25 of whom, including one additional infant with severe gastric hypoplasia, had some form of stenosis or atresia. Intestinal atresia or stenosis was found 7 times and imperforate anus 10 times, the two conditions occurring together in 2 infants. One of 10 infants with tracheoesophageal fistula also had an imperforate anus.

Hypoplasia of the lungs was seen only 3 times, in association with one case each of unilateral renal agenesis, hypoplasia, and ectopia. Abnormalities of the central nervous system and eye occurred in 23 cases; the most frequent cerebral anomaly was some form of hypoplasia. Abnormalities of the musculoskeletal system, including abnormal facies and cleft palates, were also frequent, but did not show any pattern in their distribution.

DISCUSSION

In this survey we have attempted to delineate patterns of malformation rather than to establish clinicopathological correlations. Although we cannot evaluate the genetic background of these anomalies, we hope to provide some basis for the separation of primary developmental and secondarily acquired abnormalities. In this sense, we regard primary developmental abnormalities as aberrations in the differentiation of primitive tissue into organ systems, by virtue of either deficient anlage or distorted organization. We consider secondarily acquired abnormalities as those superimposed upon recognizably differentiated, but incompletely

Table III. The occurrence of urinary tract anomalies with "congenital" nephritis and certain abnormalities of the lower urinary tract

	Total No. of cases	*Associated urinary tract anomalies*																	
		Kidney						*Ureter*						*Bladder and urethra*						
		Unilateral agenesis	*Simple hypoplasia*	*Dysplastic hypoplasia*	*Ectopia*	*Duplication*	*None*	*Atresia*	*Stenosis*	*Megaureter*	*Duplication*	*Ureterocele/ectopia*	*None*	*Exstrophy*	*Vesical fistula*	*Megacystis*	*Posterior urethral valve*	*Bladder neck obstruction*	*Urethral atresia*	*None*	*No associated anomaly*
A. "Congenital" nephritis.																					
Pyelonephritis																					
Acute	9						9						9							9	9
Chronic	11		1	3			7		1	1		2	7			3				8	0
Glomerulonephritis																					
Acute	2						2						2							2	2
Chronic	3						3						3							3	3
Medullary and cortical necrosis	5						5						5							5	5
B. Vesical anomalies.																					
Exstrophy	1			1			0	1					0	×						–	0
Megacystis	8		1				7			8			0			×				–	0
C. Vesical neck obstruction.																					
Posterior urethral valves	18			9			9						18				×			–	9
Urethral atresia	2			2			0	2					0						×	–	0
Urethral stenosis	1			1			0						1					×		–	0
D. Deficient abdominal muscle.	4			1			3			2			2			2	1	1			0

formed, organ systems. With this in view, the study has been limited to autopsy cases with urinary tract malformation, regardless of cause of death.

Simple and dysplastic hypoplasia. A large proportion of this group, approximately a third, had simple hypoplasia of the kidneys. This abnormality was infrequently associated with other anomalies of the urinary tract, but malformations of other organ systems, on the other hand, were present in 32 of the 58 cases. Although hypoplasia is not a well-defined concept, we have based our selection on renal weight. It is difficult to relate renal mass to functional capacity, and the ability of human beings and experimental animals to survive with markedly decreased amounts of renal parenchyma is well known. At times of relatively rapid body growth, however, a deficiency of renal mass may impose severe functional restrictions, and a small kidney that is able to function in normal situations may not be able to respond to abnormal, extrarenal stress, such as diarrhea and dehydration.

There appear to be at least three possible mechanisms in the pathogenesis of simple hypoplasia: the organization of less than the usual amount of nephrogenic tissue may result in kidneys that have fewer than the normal number of reniculi; kidneys that have reached their maximal development relatively early in fetal life may lack the last generation of nephrons that would normally form; and finally, both intrinsic and extrinsic factors may retard the growth of kidneys that are endowed with a full complement of nephrons.

There is the possibility that compensatory enlargement of existing nephrons may lead to normal renal mass despite a paucity of functional units. (Such cases might not, of

course, have been included in this series, in which renal weight was the primary criterion of simple hypoplasia.) This condition may occur, for example, in association with cyanotic heart disease, in which abnormal glomerular enlargement has been described.[15] There is no obvious explanation for the failure of the normal nephrons in a hypoplastic kidney to undergo hypertrophy. Although it is theoretically possible for a kidney with simple hypoplasia, no matter what the cause of retarded growth, to overcome its initial disadvantage, morphologic hypertrophy has, in general, not been seen in the kidneys included in this study.

Kidneys with dysplastic hypoplasia had an obvious structural aberration, in contrast to those with simple hypoplasia, although both had in common a decreased amount of renal parenchyma. There was a high incidence of associated urinary tract malformation in dysplastic hypoplasia and, in comparison with simple hypoplasia, a lower incidence of anomalies of other organ systems. Dysplastic hypoplasia was usually associated with obstruction to urinary flow. Dysplasia in this series covered a spectrum ranging from profound parenchymal disorganization to focal microscopic maldevelopment. Focal dysplasia was not observed by itself, but was always seen in association with other urinary tract abnormalities. The type of dysplasia often seemed to be related to the type of obstruction. The multicystic kidney, for example, has been seen in this group only with ureteral atresia (though not all ureteral atresia has been associated with a multicystic kidney); posterior urethral valves have been associated predominantly with cortical dysplasia.

If, as it appears, the presence of renal dysplasia suggests urinary tract obstruction, it is not unexpected that ureteral obstruction was largely associated with ipsilateral, and lower urinary tract obstruction with bilateral, dysplasia. The multicystic kidney, with its atretic ureter, would seem to represent a disorganization of renal development which began with the initial differentiation of the metanephros. The cortical dysplasia seen with posterior urethral valves, on the other hand, is an abnormality of the peripheral cortex, affecting the last generations of nephrons but leaving the central portions of the cortex relatively unaltered. This structural relationship suggests that the dysplasia dates from the inception of function and the development of significant "backpressure." It is also conceivable that some dysplastic changes may be the result of inflammation and scarring,[16] but the concensus[7, 8] is that even focal areas of dysplasia are developmental abnormalities which predispose to infection and scarring.

Congenital nephritis. Certain types of nephritis have been included in this survey in order to evaluate their relationship, if any, to underlying malformation. Pyelonephritis is perhaps the most likely to be regarded as having an association with malformation. Porter and Giles[17] have described tubular abnormalities, which they regard as congenital, in cases of pyelonephritis during very early infancy, and Marshall[7] and Ericsson and Ivemark[8] have described renal dysplasia underlying inflammation and scarring.

On the assumption that acute or chronic renal infection which developed so early in life might be related to a *locus minoris resistentiae*, 20 infants who had pyelonephritis in the first 3 months of life were studied. The series included 9 acute cases, none of which had any gross or microscopic urinary tract abnormality that might have predisposed to infection. In this particular group the acute infections appeared to have developed during the course of *Escherichia coli* septicemia,[18] although it is reasonable to assume that acute or suppurative pyelonephritis might be associated with obstruction in other cases. The chronic cases, on the other hand, were all associated with some form of urinary tract malformation. Many of the latter were, as might be expected, obstructive, but the group also included some primary renal dysplasia without lower urinary tract obstruction. The factor of intrarenal obstruction cannot, of course, be excluded, and dysplasia might have

abetted the localization of bacteria in the kidney. There is still the possibility that some of the chronic inflammation in association with dysplasia represents vascular or local obstructive change, rather than a bacterial pyelonephritis lenta.

Glomerulonephritis or the nephrotic syndrome in relation to malformation is more speculative, but the nephrotic syndrome, when it occurs in the first year of life, may be suspected of having a familial or "congenital" basis.[21, 22] This syndrome, which seems to be associated with glomerular alterations similar to those observed in older children with the nephrotic syndrome,[22] may be due to congenital glomerular abnormalities resulting from maldevelopment or intrauterine injury. Another form of glomerular alteration observed in early infancy is the scarring and involution known as "glomerulosclerosis." One of the 3 infants with the nephrotic syndrome in this series had severe glomerular scarring that could be regarded as "congenital glomerulosclerosis," and, during the course of glomerular involution and obsolescence, alterations that could account for proteinuria and the nephrotic syndrome might have occurred. In the other 2 cases of the nephrotic syndrome the histologic appearance was that of membranous glomerulonephritis, which is like the alterations seen in older children.

Finally, ischemic renal necrosis occurring in the first few days of life has been included because of the possibility of associated vascular malformation. Patients who have survived for a period of time seem to have developed hypertension,[23] but no intrinsic or underlying arterial anomaly has been uncovered. These patients, as a group, suffered from anemia, and the renal necrosis is regarded as a complication of fetal anoxia and shock.

Genitourinary syndromes. A group of relatively common lower urinary tract anomalies that might be encountered in clinical practice was selected from the autopsy series and was evaluated with reference to anomalies of the upper urinary tract. Malformations of the kidney and ureter, often clinically mute, play an important role in the eventual outcome of more easily recognized conditions of the lower urinary tract. While it is generally recognized that pyelonephritis can complicate obstructions of the lower urinary tract, dysplasia as a cause of renal failure may be overlooked.

There were 29 infants with infravesical obstruction, in all of whom the condition was diagnosed or suspected before death. Surgical intervention, while relieving the obstruction in some of these children, was unsuccessful in averting a fatal outcome due to renal failure. Many had chronic urinary tract infection, but dysplasia was also an important factor in the failure to reverse the functional decline. Renal dysplastic changes were seen most often in association with posterior urethral valves. These alterations were predominantly cortical in location. Medullary alterations were also frequently encountered and were often difficult to attribute exclusively to either dysplasia or the scarring of chronic infection and hydronephrosis. The medullary alterations could have been the combined effect of scarring and dysplasia. In cases of the megaureter-megacystis syndrome, on the other hand, renal dysplasia occurred infrequently.

Our observations in the syndrome of deficient abdominal musculature are in accord with the oft-repeated view that this condition is related to bladder neck or urethral obstruction. This position is strengthened by our finding of a definite valve in the posterior urethra of one infant. We do feel that this condition is related to lower urinary tract obstruction, even though an anatomic stricture cannot always be found.

Anomalies of other systems. Over two thirds of the infants with primary renal anomalies were also found to have malformations of other organ systems. Any study involving the pediatric age group might reasonably be expected to demonstrate a high incidence of congenital anomalies; the frequency with which they occurred in this series is, however, unusually high, far greater than in the autopsy series as a whole. The

fact that renal abnormalities were usually associated with other anomalies tends to confirm the commonly held belief that the presence of one malformation increases the probability of the presence of others.

Anomalies of the cardiovascular system and the alimentary tract were those found most often with renal anomalies. The incidence of alimentary tract atresia and stenosis, in particular, was six times that in the autopsy population at large. Imperforate anus was frequently observed and was seen in combination with duodenal stenosis and tracheoesophageal fistula.

Cardiovascular abnormalities were modestly increased in incidence over the expected figure; among these, as might be expected, interventricular septal defects were most common. In dysplastic hypoplasia, however, aortic coarctation was the most common, occurring in over two thirds of the cases associated with cardiovascular malformations.

In an attempt to establish a unified pathogenesis for multiple malformations many authors have suggested a fetal insult or injury that is localized in time and that would simultaneously affect several organ systems at a critical stage in their development. It is known that the sixth to eighth week of embryonic development is a period of crucial differentiation for many organs. During this time, for example, the aortic arches undergo transformation, the cloacal membrane ruptures, the interventricular septum closes and the metanephros, potentiated by the ureteric bud, becomes differentiated into its ultimate form. Any injurious agent—infectious, metabolic, physical, etc.—is capable of inflicting widespread damage.

Our observations would in general conform to this view, but there remains the possibility that some of these malformations are interdependent in their pathogenesis. The striking coincidence, for example, of aortic coarctation with dysplastic hypoplasia is lacking in other groups of renal malformation. Simple hypoplasia, if it is the result of defective development in later fetal or even in postnatal life, can be secondarily related to the nonrenal malformations that are so often associated with it.

This sort of study leaves many questions unanswered. The roles of renal vascularity and developing function in fetal life have to be evaluated experimentally. This study does emphasize the need for experimental and finer morphologic investigation of the apparent association between dysplasia and urinary tract obstruction, of the patterns of fetal glomerular and medullary scarring, and of the effect of focal atrophy or cicatrization on the remainder of the developing kidney.

SUMMARY AND CONCLUSIONS

One hundred and eighty-one cases of congenital urinary tract abnormality have been classified and evaluated with respect to renal and associated malformations. Simple and dysplastic renal hypoplasia, occurring in 58 and 31 cases, respectively, was the most common abnormality of renal structure. Simple hypoplasia, defined as a significant reduction in otherwise normal renal mass, could be characterized as occurring frequently in association with nonrenal anomalies but infrequently with other urinary tract malformations. Dysplastic hypoplasia was also associated, though in smaller proportion, with nonrenal malformations, but other urinary tract malformations were extremely common.

Several other correlations became apparent: the association of the multicystic form of dysplasia with ureteral atresia, the occurrence of cortical and/or medullary dysplasia in half of the children with posterior urethral valves, the occurrence of half of the cases of aortic coarctation in association with dysplastic hypoplasia, the very frequent association of renal ectopia with multiple system malformations, and the relatively frequent coincidence of polydactylism and renal duplication. Cardiovascular and alimentary tract malformations occurred with significantly greater frequency in the children with renal malformations than in the autopsy series as a whole; for example, alimentary tract obstructions such as tra-

cheoesophageal fistula, intestinal atresia or stenosis, and imperforate anus, were six times as frequent.

Certain forms of nephritis in very early infancy, such as acute pyelonephritis, glomerulonephritis and the nephrotic syndrome, and cortical or medullary necrosis, were not associated with other malformations. Chronic pyelonephritis, as might be expected, was often present in association with obstruction of the lower urinary tract and was occasionally the cause of progressive renal failure. A factor of even greater moment in determining the prognosis in children with posterior urethral valves was renal dysplasia, which occurred in half the group and which vitiated surgical relief of the obstruction. Renal dysplasia was distinctly less common in association with other types of infravesical obstruction. Deficiency of the abdominal musculature was seen 4 times with bladder neck or urethral obstruction, and once in association with an actual urethral valve.

The pathogenesis of renal dysplastic hypoplasia may be related to urinary tract obstruction; however, the multicystic variety of dysplasia, which was constantly associated with ureteral atresia, was disorganized to such an extent that the renal malformation probably began with the initial differentiation of the metanephros. The peripheral type of cortical dysplasia that was observed in association with posterior urethral valves may, on the other hand, reflect the effect of urinary obstruction on a kidney that has begun to function. Finally, maldevelopment of several organ systems may result from the action of a single noxious agent during a crucial period of embryogenesis; however, the association of simple renal hypoplasia with extrarenal malformations may indicate that development of the kidney may be affected by abnormalities in other organ systems.

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Griseofulvin therapy in tinea capitis

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GRISEOFULVIN was first isolated by Oxford and co-workers,[1] in 1939, from *Penicillium griseofulvum dierckx*. As the newly discovered substance showed no antibacterial activity, it soon passed into obscurity. A "rediscovery" of griseofulvin occurred in 1947, when Brian[2] announced the isolation of a new antibiotic from *Penicillium janczewski*. He referred to this substance as the "curling factor" because its addition to fungus cultures resulted in shriveling and stunting of fungal hyphae. Brian, however, did not realize that his "new substance" was griseofulvin, until Grove and McGowan[3] identified it as such later the same year. Griseofulvin soon became widely used against fungal disease in both horticulture and veterinary medicine. Another decade went by before Gentles,[4] exploring the possibility of using griseofulvin as an antifungal agent in man, demonstrated its action against dermatophytes in experimentally infected guinea pigs. The success of this experiment finally led to world-wide trials of griseofulvin, which were pioneered by Riehl[5] in Austria, Williams and co-workers[6] in Great Britain, and Blank and Roth[7] in the United States. Clinical studies have shown that griseofulvin is useful in tinea capitis, barbae, corporis, cruris, and pedis, and in onychomycosis. It exerts a fungistatic effect upon species of Trichophyton, Epidermophyton, and Microsporon. This report presents the findings in 58 cases of tinea capitis treated on the Pediatric Service at the Baltimore City Hospital.

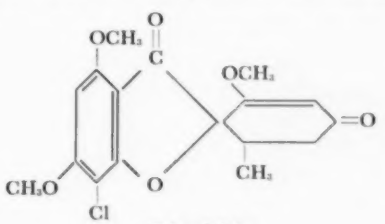
From the Pediatric Division, Baltimore City Hospital and The Johns Hopkins University School of Medicine, Baltimore.

Griseofulvin used in this study was furnished, in the form of Fulvicin tablets, by G. Kenneth Hawkins, M.D., Department of Clinical Investigation, Schering Corporation, Bloomfield, N. J.

**The Children's Hospital, 3700 California Street, San Francisco 18, Calif.*

CHEMISTRY

Griseofulvin is obtained from *Penicillium griseofulvum dierckx, P. janczewski,* and *P. patulum*. Griseofulvin is 7-chloro-4:6-dimethoxycoumaran-3-one-2-spiro-1′-(2′-methoxy-6′-methylcyclohex-2′-one-4′-one), and has the following structural formula:



Griseofulvin

The empirical formula of griseofulvin is $C_{17}H_{17}O_6Cl$. It is obtained as a white powder or needlelike crystals, and maintains its stability in its dry form for 20 months at 38° C.

MATERIALS AND METHODS

During the past 8 months we have studied the effect of griseofulvin in 58 tinea capitis

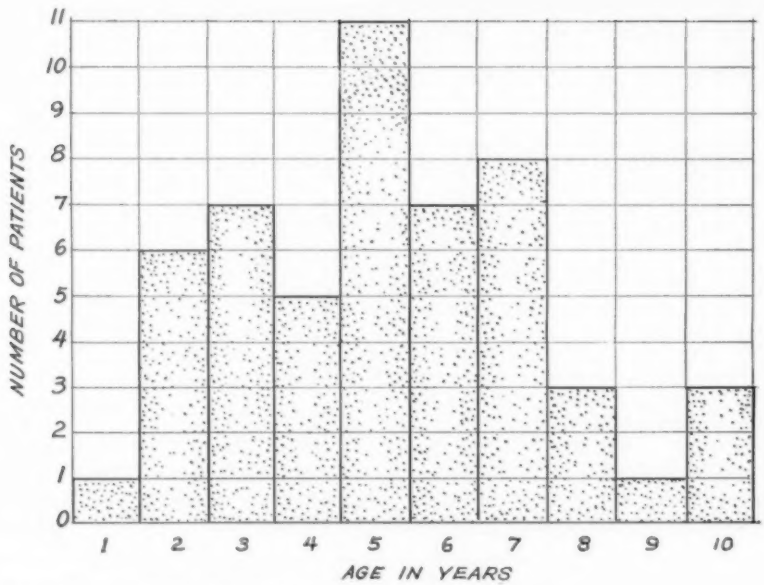


Fig. 1. *M. audouini* incidence in relation to age in 52 patients.

patients, 46 males and 12 females, ranging in age from 1 to 12 years. Of the 58 patients with tinea capitis, 52 had *Microsporon audouini* infection and 6, *Microsporon canis* infection. Fig. 1 illustrates the incidence in relation to age in the 52 patients with *M. audouini* infection. Three patients had concomitant fungus infections of the glabrous skin. Duration of the disease varied from 1 month to several years. Fifty-six of these patients were Negro and 2 were white.

All patients who came to our service with suspected lesions of tinea capitis were examined under Wood's light to determine whether the typical bluish-green fluorescence generally seen in *M. audouini* and *canis (lanosum, felineum)* infections were present. Since some of these cases may not fluoresce under Wood's light, all patients were also studied mycologically. After thorough cleansing of the lesions with a 70 per cent alcohol solution, scrapings were obtained and cultured on Mycosel* agar.

Following incubation, colonies were examined microscopically. If positive results were obtained, the material was then subcultured on Mycophil agar for final differentiation. Using this technique, we diagnosed 52 cases as due to *M. audouini* and 6 as due to *M. canis.* Serial cultures were performed during griseofulvin therapy, and patients were considered clinically cured after at least 2 successive cultures and 2 Wood's light examinations yielded negative results. The importance of these laboratory procedures to confirm clinical diagnosis cannot be overemphasized since tinea capitis lesions may mimic in clinical appearance a host of nonfungal conditions, such as alopecia and seborrheic dermatitis, in which griseofulvin is of no value. The cultural characteristics of the fungi are shown in Figs. 2 and 3.

To assure early detection of any evidence of toxicity, complete blood counts, urinalyses, and kidney and liver function tests were performed prior to institution of, and at regular intervals during, griseofulvin therapy. Several dosage schedules were used: Children weighing less than 50 pounds were given 250 mg. of griseofulvin twice or 3 times a day; those

*Baltimore Biological Laboratories, Inc.

weighing over 50 pounds were given 250 or 500 mg. 3 times or 4 times a day, i.e., the adult dosage. Some children were started on the lower dosages and subsequently switched to higher doses if after 3 to 4 weeks progress was not satisfactory. Patients were not shaved or epilated. Patients were instructed to return every 2 weeks for follow-up; intervals were longer at times, however, as a result of failure to keep appointments.

RESULTS

With the exception of 2 cases which cleared completely within 3 weeks, no significant improvement was seen during the first 2 weeks of therapy. Fluorescence generally had faded substantially and hairs had become more resistant to manual epilation or shaving by the fourth week. At that time, increased scaling over the affected areas and regression of lesions were also noted in most cases. Clinical cure based on the previously described criteria was obtained within 3 weeks in 2 patients, within 4 to 6 weeks in 12, and within 7 to 10 weeks in 30; the remaining 14 cases required 11 weeks or more of treatment. In the 3 patients with concomitant involvement of the glabrous skin, the tinea corporis cleared simultaneously with the tinea capitis. There were no failures. The results of treatment are summarized in Table I, and examples of the clinical response are illustrated in Figs. 4*A* through 5*B*.

Toxicity. There was only one instance of apparently serious toxicity due to griseofulvin among the 58 patients included in this study. This was an instance of marked leukopenia, which will be discussed separately. There were 9 instances of temporary leukocyte depression below 5,000 per cubic millimeter. However, the white blood count of these patients rebounded while they were receiving griseofulvin therapy. There were also 2 instances of transient maculopapular rashes accompanied by pruritus. The rashes disappeared when the patients were taken off griseofulvin and placed on an antihistamine or a topical antiallergic agent and did not recur when griseofulvin therapy was reinstituted. One patient complained of a temporary headache. There were no other signs of toxicity attributable to griseofulvin in our series.

Case report. The case of this patient is discussed in detail because he was the only one who had a serious toxic reaction during treatment with griseofulvin, and because his leukopenia was reinduced by re-treatment with this agent. This 8-year-old Negro male who had enjoyed good general health was referred to the Out-Patient Department of the Pediatric Service with a tentative diagnosis of tinea capitis. Diagnosis was confirmed by examination with Wood's light and a positive culture for *M. audouini*. The patient was placed on griseofulvin, 250 mg. twice a day. Two weeks later he developed an extensive rash. At this time, griseofulvin

Fig. 2. *M. audouini* culture.

Fig. 3. Photomicrograph of *M. canis* culture.

was discontinued orally and a topical griseofulvin lotion prescribed. After 10 days, the rash had disappeared and the patient was again placed on oral administration of griseofulvin, 250 mg. 2 times a day. On examination, 3 weeks later there had been no recurrence of the rash, and the tinea capitis lesions were improved.

The patient was seen again 3 weeks later, at which time there was no fluorescence under the Wood light and new hair growth had started. Two weeks later, Wood's light examination was again negative as was the culture. At this time, however, the patient showed a sudden drop in the white blood count to 2,500, with 40 per cent polymorphonuclear leukocytes and 60 per cent lymphocytes. In view of this leukopenia and since the tinea capitis appeared clinically cured, griseofulvin was discontinued. The patient was re-examined 6 days later, at which time his white blood count had risen to 4,300, with a normal differential count. After an additional 6 days the white count was 5,300. At this time, it was decided to admit the patient to the hospital and challenge him with griseofulvin to establish whether his leukopenia was due to this agent.

Fig. 4*A*. *T. capitis (M. audouini)* in young female.

Fig. 4*B*. Lesion following 3 weeks of griseofulvin therapy.

Fig. 4*C*. Apparent healing after 12 weeks of griseofulvin therapy.

On admission the patient was found to be a well-developed, well-nourished Negro male; his family and personal histories were noncontributory. Physical examination showed him to be in good health. The white blood count was 5,600 per cubic millimeter with 60 per cent polymorphonuclear leukocytes and 2 per cent eosinophils. Tuberculin, intermediate strength, and a sickle cell preparation were negative. Two bone marrow smears were normal. Urinalysis proved negative. During the first day of hospitalization the patient had an unexplained rise in temperature, which subsided spontaneously. Admis-

Table I. Results in 58 cases of tinea capitis (52 *M. audouini* and 6 *M. canis*)

	No. of cases	
Cleared		
Within 3 weeks	2	
Within 4 to 6 weeks	12	
Within 7 to 10 weeks	30	
Within 11 weeks or more	14	
Leukocyte depression		
Below 5,000	5	
Below 4,000	4	
Below 3,000	1	
Side effects	2	temporary maculopapular rashes
	1	periorbital edema

istration of griseofulvin, 250 mg. 3 times a day, was begun on the third hospital day. No untoward effects, except a mild depression of the white blood count to 4,000 to 5,000, were noted until the fifth day of therapy on which the white blood count dropped to 3,000, with 37 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 2 per cent basophils, 58 per cent lymphocytes and 2 per cent monocytes. A bone marrow aspiration at this time was considered normal. Griseofulvin was discontinued the following day. On the morning following discontinuation of therapy, the patient had a white blood count of 2,800, with 33 per cent polymorphonuclear leukocytes, 2 per cent eosinophils, 7 per cent basophils, 55 per cent lymphocytes, and 3 per cent monocytes. It was decided to administer no additional griseofulvin and to keep the patient under observation. The leukocyte count began rising steadily with concurrent appearance of eosinophils and disappearance of basophils. At discharge, the white blood count was 4,500, with 35 per cent polymorphonuclear leukocytes, 5 per cent eosinophils, no basophils, 53 per cent lymphocytes, and 6 per cent monocytes. The temporary leukopenia was diagnosed as a reaction to griseofulvin. The rapid rise in the white blood count following withdrawal of griseofulvin suggests that irreversible agranulocytosis does not appear to be a problem with this antibiotic, at least if the complication is recognized promptly.

DISCUSSION

Our findings confirm those of other investigators[8, 9] who have reported that griseofulvin is most effective in tinea capitis. When given in adequate doses for sufficient periods of time, that is, until at least 2 consecutive cultures and Wood's light examinations have proved negative, griseofulvin will eradicate tinea capitis. Prior to institution of griseofulvin therapy, diagnosis should be confirmed by laboratory procedures to avoid the use of this compound in such nonfungal conditions as alopecia or seborrheic dermatitis or in *C. albicans* infections where it can be detrimental.

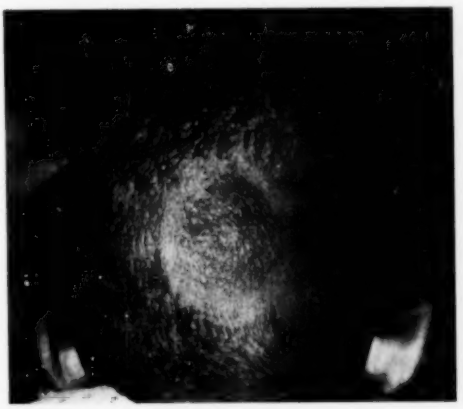


Fig. 5*A*. *T. capitis (M. audouini)* in young male.

Fig. 5*B*. Result after 4 weeks of griseofulvin therapy.

In those cases in which *M. canis* is the offending pathogen, treatment or removal of the infected animal is absolutely necessary to avoid continual reinfection of the patient. If the child comes from a large family, it is advisable to examine all his prepubertal siblings to ascertain whether the infection has been transmitted to any of them. If, after these measures are taken, the child fails to improve or has a reinfection, the possibility of the presence of an infected animal in the neighborhood should be investigated.

With the availability of griseofulvin, the previously employed topical agents and the potentially dangerous roentgen epilation should no longer be used. It is too early to determine whether reinfections or relapses occur in patients who have been cured with griseofulvin.

SUMMARY

1. The oral treatment of tinea capitis due to *M. audouini* or *M. canis* was studied in 58 patients.

2. Griseofulvin was given orally in doses ranging from 250 mg. twice a day to 500 mg. 4 times a day, depending on the weight of the patient and the severity of the fungus infection.

3. Patients were carefully followed with serial Wood's light examinations and cultures to observe the therapeutic effect of griseofulvin, and with urinalyses, serial blood counts, and hepatic and renal function tests to determine its possible toxicity.

4. Griseofulvin proved uniformly effective, achieving eradication of the fungus infection in all 58 cases included in this study.

5. The only adverse reactions observed were 9 cases of transient leukopenia, 8 of which rebounded during therapy and 1 following its discontinuation, 2 cases of transient maculopapular rash, and 1 case of temporary headache.

My thanks are due to Dr. Harold E. Harrison for his encouragement and invaluable help which made this study possible, and to Donald Tonelli, M. A., for his technical assistance.

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Chylous cysts of the mesentery in infants

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MESENTERIC cysts form an interesting group of rarely encountered abdominal tumors. Benevieni,[1] the Florentine anatomist, is generally believed to have described the first case in 1507 in an autopsy performed on an 8-year-old boy. Rokitansky[2] in 1842 described a chylous cyst also found at autopsy. Pean[3] in 1883 first successfully treated this condition when he marsupialized a cyst and the patient recovered. Carson[4] in 1890 recorded the first case noted in the United States. Since that time, isolated case reports and small series have been reported. Gross[5] reported 12 cases of isolated mesenteric cysts, and his series, with the excellent reports of Vaughn, Lees, and Henry,[6] Steinreich,[7] and Burnett, Rosemond, and Bucher[8] have been important contributions in recent years.

Considerable confusion has prevailed in the differential diagnosis of cysts of the mesentery but these recent papers have well differentiated mesenteric cysts from enteric cysts or duplications of the intestinal tract, omental cysts, and cystic lesions of retroperitoneal origin. At times, differentiation from enteric cysts is difficult, although most of the latter have a well-differentiated muscular wall and a mucous membrane resembling some portion of the intestinal tract. This presence of elements of intestinal mucosa in a cyst wall is significant in the differential diagnosis, as noted by Warfield.[9] Dermoid cysts usually show types of skin appendages in the structure of the wall or contents.

True mesenteric cysts are of two general types, serous or chylous, depending upon the type of fluid contained. Mesenteric cyst of any type is extremely rare, Roller[10] and Burnett and co-workers[8] considering it the rarest of all abdominal tumors. In a review of the literature in 1950 they were able to find only 200 cases. Slocum[11] reported only 6 cases at the Massachusetts General Hospital for the years 1900 to 1926. Beahrs and Judd[12] reported 7 cases in over one million patients seen at the Mayo Clinic. Moore[13] reported 4 cases from the Indiana Medical Center in 20 years. One case was seen in 160,000 admissions to the Jewish Hospital, Philadelphia.[14] The two largest series reported to date are those of Gross who found 12 cases in the Boston Children's Hospital, and Steinreich who reported 8 cases from Akron, Ohio.

The chylous variety of mesenteric cyst makes up a small percentage of the cysts encountered. Five of Gross's cases were chylous, and there were 2 containing chylous material in the series reported by Steinreich. Cysts may be found at any age. Burnett[8] in his review found them commonest in the years from 1 to 10, although they occurred

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Fig. 1. Upright film of abdomen showing gas-filled loop of jejunum (Case 2).

throughout the life span. They are relatively uncommon, however, in infancy. Burnett's series showed 5.5 per cent at ages less than 1 year, while Gross had 5 infants in his series. Warfield reported 9 of 129 cases of mesenteric cysts in infants. The distribution as to sex is reported by Burnett in a series of 200 cases as 33.5 per cent male, 54.5 per cent female, and 12 per cent unknown.

The clinical findings and symptomatology are varied. The typical case presents slow enlargement of the abdomen, in many cases asymptomatic. There may be recurring attacks of mild to moderate abdominal pain. In some cases there was reduced appetite and failure to gain weight. Intestinal obstruction may occur in rare instances as a result of angulation of the intestine by the cyst or from pressure. The physical examination in the patient without obstruction may show an abdominal mass. At times the cyst may be so flabby that only an ill-defined thickening or shifting fluid wave may be present. Radiologic examination of the abdomen may show a gasless shadow displacing the intestine and, in the case of obstruction, the dilated bowel of intestinal obstruction.

It is usually possible to dissect the cyst out of the mesentery without interfering with the circulation of the intestine. If this is possible, it is considered the operation of choice. Rarely, intestinal resection may be necessary. Marsupialization has been used in the past but is not considered a recommended form of therapy.

This presentation concerns 2 cases of chylous cyst of the mesentery encountered during a 25 month period at the Danbury Hospital, Danbury, Connecticut. These cases are unusual in that they occurred in early infancy, one patient being 4 days of age and the other 3 months of age. In the 4-day-old patient, the chylous cyst of the high ileal mesentery was an incidental finding at operation for malrotation of the colon, volvulus of the midgut, and duodenal obstruction. Bentley and O'Donnell[18] have recently reported 4 cases of mesenteric cysts associated with malrotation of the intestine and discuss the possibility of their relationship especially when they occur together in infancy and early childhood. Our 3-month-old patient presented with acute intestinal obstruction due to a large chylous cyst in the mesentery of the upper jejunum. In both cases it was possible to remove the cyst surgically without resection of the intestine.

CASE REPORTS

Case 1. Patient D. C. was born at the Danbury Hospital, March 22, 1956, by a full-term normal spontaneous pelvic delivery, and in neonatal examination showed no abnormalities. At the end of the second day of life, the baby was noted to be regurgitating large amounts of mucus. Two yellow stools had been passed. When seen

in consultation on the fourth day there was distention of the upper abdomen with flatness of the lower abdomen. No masses were felt. X-ray of the abdomen revealed gaseous distention of the stomach and duodenum; no gas was visualized beyond the third portion of the duodenum. Operation performed on this day revealed malrotation of the colon with volvulus of the midgut and a cystic yellow mass of dumbbell shape protruding from either side of the small bowel mesentery of the upper ileum. The mass was approximately 2 cm. in diameter at each pole. After detorsion of the midgut volvulus and division of the membrane attaching the cecum to the right posterior peritoneum, excision of the chylous cyst was performed by dissecting the mass free from the mesentery and small bowel. The postoperative course was without difficulty, and the child has developed normally in the ensuing 4 years. Pathologic examination revealed chylous fluid in a fibrotic cyst wall with no evidence of smooth muscle or mucosal element.

Case 2. Patient E. B., Jr., was admitted April 11, 1958. This 10-week-old infant was born by normal spontaneous pelvic delivery and progressed normally through the neonatal period except for occasional colic. Twenty-hour hours prior to admission vomiting began which was persistent and projectile. It was noted to be bile stained. There were no stools in the 24 hours prior to admission. When first seen, the child was well-developed but dehydrated. The abdomen was soft, not distended, but within the abdomen there was a rounded and slightly sausage-shaped movable mass in the right lower quadrant approximately 10 by 4 cm. in size. This mass was tense and dull to percussion. Rectal examination was negative; the white blood count was 10,950 with a normal differential. X-ray studies of the abdomen showed one distended jejunal loop (Fig. 1). Following hydration, laparatomy was performed. There was a large yellowish chylous cyst of the mesentery filling approximately two thirds of the abdomen and extending through the mesentery of the upper jejunum (Figs. 2 and 3). The jejunum was stretched tightly over the mass, producing obstruction. The proximal jejunum was dilated; the distal jejunum collapsed. It was possible to dissect the mesenteric cyst from the intestine and mesentery without compromising the intestinal circulation. The small bowel obstruction was thus relieved. The postoperative course was quite satisfactory and the child has remained well during the ensuing 2 years.

Pathologic examination revealed chylous fluid content. The wall of the cyst was found to be composed of an inner layer of endothelium beneath which were noted myxomatous cells and collagen fibers. There were no muscle or mucosal elements noted.

Fig. 2. Chylous cyst lying through mesentery of jejunum, causing obstruction of this jejunal segment (Case 2).

Fig. 3. Dilated proximal bowel and collapsed distal bowel are shown here. Obstruction due to chylous mesenteric cyst (Case 2).

DISCUSSION

It is interesting to note that two examples of an extremely rare condition—chylous mesenteric cyst in early infancy—were encountered within a 25 month period in a moderate-sized (180 beds) general hospital. The literature has stated that the mortality is high when volvulus is associated with mesenteric cyst; however, in Case 1 the cyst was an incidental finding in an otherwise classical case of malrotation of the colon with midgut volvulus. Treatment of the primary condition with incidental removal of the cyst led to a successful outcome. One may conjecture as to the association of two types of intestinal anomaly in this patient and reiterate the opinion of many that exploration of the entire tract may be rewarding when one intestinal anomaly is present.

Case 2 presents the relatively rare clinical picture of acute intestinal obstruction due to mesenteric cyst. In this case, high jejunal obstruction with rapid dehydration and very little abdominal distention was presumably caused by relatively rapid increase in size of the mesenteric cyst. This child had had occasional colic in his 10 weeks of life but frequent abdominal examination had failed to reveal any abnormality until acute symptoms of obstruction began.

The etiology of mesenteric cysts has been debated for many years and is still not definite. Ewing[15] described them as chylangiomas, like lymphangiomas in other portions of the body, consisting of endothelium and connective tissue. Warfield, Gross, and Beahrs concur in the view that these are preformed cystic masses due to displaced lymphatic tissue. Some writers have felt that the cysts arise from obstruction of normal channels and may be acquired, others that they may appear by rupture of normal lymphatic channels. The presence of well-formed chylous cysts at the early ages in the 2 cases reported supports the theory of congenital lymphatic cystic rests.

SUMMARY

Isolated mesenteric cysts form an interesting and rare group of abdominal tumors. They are presumed to arise from congenital bits of lymphatic tissue misplaced in the mesentery. A relatively small proportion of the total number of the mesenteric cysts contain chyle. These cysts may be found at any age and are relatively unusual in infancy. They present with abdominal swelling, occasional bouts of pain and nausea, and may rarely cause intestinal obstruction. Two cases of chylous mesenteric cysts in infancy are reported here. In one the cyst was an incidental finding in a case of malrotation and volvulus; in the second the cyst caused acute intestinal obstruction. Both cases were successfully managed by excision of the mesenteric cyst without intestinal resection.

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Recovery from Salmonella meningitis after treatment with furaltadone (Altafur)

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FURALTADONE (Altafur),[1] a nitrofuran derivative, was recently added to the armamentarium of antimicrobial agents. Limited experience to date suggests that this drug is effective in the treatment of certain infections due to susceptible micro-organisms. Recently, we observed recovery from Salmonella meningitis of an infant treated intravenously with this compound. Since search of the literature failed to disclose information on furaltadone therapy in Salmonella meningitis, it is deemed of interest to present this brief report.

REPORT OF THE CASE

C. D., a 3-week-old, white male infant, was admitted to the Buffalo Children's Hospital on May 1, 1960, because of lethargy and seizures. He had been well until one day prior to admission, when he refused feedings. On the day of admission he became lethargic, vomited, and had 2 seizures.

The past history was unremarkable. He was the product of a full-term, uncomplicated pregnancy and delivery. The birth weight was 2.5 kilograms. He was placed in an incubator for 2 days because of mild respiratory distress with cyanosis soon after delivery.

Physical examination showed an acutely ill and lethargic infant. The skin was ashen gray. The anterior fontanel was full, and the sutures were separated. Extremities were flaccid with hypoactive deep-tendon reflexes. The Moro reflex was absent, and the sucking reflex was poor. There were no meningeal signs. Examination of the heart, lungs, and abdomen was not notable.

The rectal temperature was 97.6° F., the pulse rate 160, and the respiratory rate 48 and irregular. The weight was 2.75 kilograms and the head circumference, 13.5 inches.

An atraumatic lumbar puncture revealed cloudy fluid. The initial pressure was 180 mm. of water and the closing pressure, 120 mm. There were 450 white blood cells per cubic millimeter with 60 per cent lymphocytes. The Pandy test was 4 plus. Gram-negative bacilli were seen on a film of centrifuged spinal fluid. The total protein was 700 mg. per cent, glucose less than 5 mg. per cent, and chloride 110 mEq. per liter. Blood glucose was 12 mg. per cent. Examination of the blood disclosed a hemoglobin of 16.3 Gm. per cent and a white cell count of 1,000, with 69 per cent lympho-

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cytes, 20 per cent segmented neutrophils, and 11 per cent bands. Intermittent intravenous therapy with penicillin (6 million units per day), sulfisoxazole (Gantrisin) (200 mg. per kilogram per day), and chloramphenicol succinate (60 mg. per kilogram per day) was begun. In an attempt to prevent future fibrosis of the leptomeninges, hydrocortisone (50 to 100 mg. per square meter per day) was administered during the first 10 days.

The cultures of spinal fluid, blood, and feces taken on admission revealed *Salmonella schwarzengrund*. The urine was sterile. Sensitivity tests of the Salmonella strain, by the use of the impregnated-disc technique, illustrated susceptibility to chloramphenicol, tetracycline, and furaltadone (Altafur), but not to penicillin, erythromycin, streptomycin, and sulfonamides. Gantrisin was, therefore, stopped. Penicillin was continued because of the presence of pneumonic patches, discovered by x-ray examination.

On the third hospital day, the temperature dropped to 95° F., seizures persisted, and neurogenic bladder developed. A repeat spinal tap revealed 5,000 white blood cells per cubic millimeter with 50 per cent neutrophils and a total protein of 785 mg. per cent. Organisms were seen on a direct film. Tetracycline (12 mg. per kilogram per day) was started. During the next several days, while on tetracycline, the patient developed severe diarrhea. Nose, throat, and stool cultures showed the presence of large numbers of *Pseudomonas aeruginosa*. Tetracycline was withdrawn, and oral polymyxin B (60 mg. per 24 hours) was administered for 10 days.

During the second week of therapy there was marked clinical improvement. The infant became alert, cried, and was able to suck. Two successive lumbar punctures revealed sterile spinal fluid with decreasing protein and cellular elements. On the fifteenth day chloramphenicol was discontinued.

In the ensuing week irritability and projectile emesis gradually developed, and the temperature spiked to 103° F. Meningeal and localizing neurological signs were absent. The white blood cell count was 18,500 per cubic millimeter, with 54 per cent neutrophils. Urinalysis was not remarkable. Roentgenograms of the skull and long bones were normal. Relapse of meningitis was suspected, and a lumbar puncture was repeated. The spinal fluid appeared grossly purulent. There were 1,750 white blood cells per cubic millimeter, with 90 per cent neutrophils. The total protein content was 470 mg. per cent and the glucose concentration was less than 5 mg. per cent. The bacterial culture grew out *Sal. schwarzengrund*, sensitive to chloramphenicol, tetracycline, streptomycin, and furaltadone.

A second course of intravenous chloramphenicol (75 mg. per kilogram per day) was instituted. Streptomycin (5 mg.) was given intrathecally once and 50 mg. twice a day intramuscularly. Human gamma globulin (4 c.c.) was administered intramuscularly. In spite of this therapy, 4 days later the spinal fluid again contained large numbers of *Sal. schwarzengrund*. It became evident that chloramphenicol, tetracycline, and streptomycin had failed to control the infection, in spite of continued in vitro sensitivity of the strain. Therefore, intravenous treatment with furaltadone in a dosage of 20 mg. per kilogram per day was started. This drug was administered in 100 c.c. of 5 per cent glucose water or of saline over a 4-hour period, once a day. There was clinical evidence of improvement during the next several days, with subsiding irritability, disappearance of seizures, and increasing appetite. The intravenous preparation was given for 8 days and furaltadone (30 mg. per kilogram per day) by mouth, was used for 4 additional days. Observed side effects were mild diarrhea and emesis. The patient had one positive spinal fluid culture, 24 hours after initiation of furaltadone therapy. Successive spinal fluid cultures were all sterile. The stool cultures, however, continued to display the presence of *Sal. schwarzengrund*. The significant findings are shown in Fig. 1.

The low spinal fluid glucose values obtained repeatedly on sterile spinal fluid re-

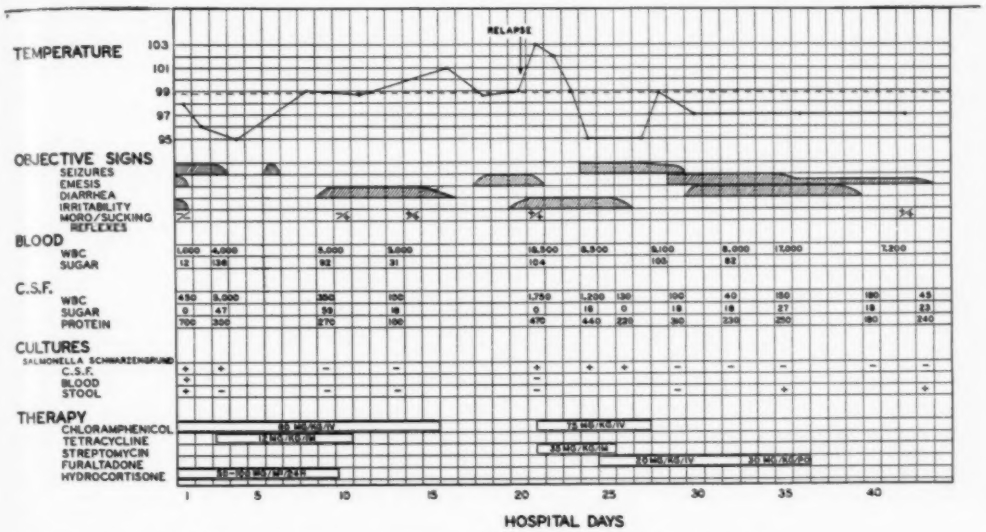

Fig. 1. Clinical and laboratory data on infant with *Sal. schwarzengrund* meningitis.

main unexplained. There was no evidence of an expanding lesion. Bilateral subdural taps, done on the fifth day of relapse, revealed the presence of 1.5 c.c. of serosanguineous, sterile fluid on each side. These taps were repeated 2 weeks later, but no fluid was obtained. An electroencephalogram done on June 8, 1960, was normal.

Epidemiologic investigation disclosed that the mother was a carrier of *Sal. schwarzengrund*. It is of interest also that the infant responded to the infection with the formation of group-specific Salmonella antibodies, as measured by the hemagglutination test.[2]

The hospital course, during the acute stages of septicemia and meningitis, was further complicated by the presence of: (1) anemia and hypoproteinemia, (2) leukopenia and thrombocytopenia, (3) hyponatremia and edema, (4) hypocalcemia, and (5) hypoglycemia. These complications were appropriately treated.

The patient was discharged on the fifty-second hospital day; he was afebrile and gaining weight. The Moro reflex was present. There was no increase in head size. The extremities were moderately spastic, and the deep-tendon reflexes were hyperactive. He was unable to follow light, but could hear noise. The possible impairment of vision more likely would be the sequela of meningitis rather than that of therapy. Mention should be made, however, of a reported allergic reaction to furaltadone, involving paresis of the lateral rectus muscles.[3] During the 2 months after discharge from the hospital there was no relapse of meningitis and the patient improved continuously.

DISCUSSION

The present case of *Sal. schwarzengrund* (Group B) meningitis with recovery after treatment with furaltadone, is unusual from several points of view. First, Salmonella meningitis is a relatively rare disease.[4] For example, during a 6 year period (1952 to 1957) of 318 cases of bacteriologically proved meningitis seen at this hospital, Salmonella meningitis was encountered in only 3 patients. Saphra and Winter[5] reviewed 7,779 human Salmonella infections isolating this pathogen from 77 cases of meningitis, indicating a 1 per cent rate of meningitis among human Salmonella infections. Second, *Sal. schwarzengrund* is only infrequently encountered in either man or animals. For example, MacCready and associates[6] recovered *Sal. schwarzengrund* only once

among 2,625 Salmonella cultures excluding *Sal. typhi.* Coleman and associates[7] isolated this organism only 10 times among 3,422 Salmonella cultures excluding typhoid bacillus. Third, the present case appears to be the first instance of Salmonella meningitis in an infant treated successfully with furaltadone.

The data presented here strongly suggest, but do not prove, that furaltadone contributed to the control of the bacterial infection. This conclusion is supported by the facts that the prognosis of this disease in the young infant in the absence of chemotherapy is poor and that several antibiotics had failed to eradicate the infection in our patient. Henderson[8] in 1948 reviewed 147 cases of Salmonella meningitis. The fatality rate was 94 per cent among patients not treated with sulfonamides or antibiotics and 52 per cent among those receiving sulfonamides. The prognosis also depends upon the age of the patient, for only 1 of 49 patients less than 1 month old recovered, whereas 17 of 80 children in the older age group survived. In view of the rarity of Salmonella meningitis in children, except during unusual epidemics, it will remain difficult to evaluate the absolute and relative merits and shortcomings of furaltadone, and, in fact, of other antimicrobial agents as well.

SUMMARY

Apparent successful therapy with furaltadone, administered intravenously, of an infant with *Sal. schwarzengrund* meningitis is described. The patient had failed to recover from the infection after previous treatment with several antibiotics. Furaltadone was tolerated rather well.

Furaltadone was kindly supplied by Eaton Laboratories, Norwich, New York, through the courtesy of Dr. Charles H. Tracy, and the Salmonella strain was typed by Dr. Joseph W. Winter, Beth Israel Hospital, New York, New York.

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Congenital aplasia or marked hypoplasia of the myocardium of the right ventricle (Uhl's anomaly)

Clinical, angiocardiographic, and hemodynamic findings

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CONGENITAL aplasia or almost complete absence of the myocardium of the right ventricle is an extremely rare malformation of the heart. The clinical and pathologic findings in this anomaly have been described only once previously.[1] This paper presents the previously unreported angiocardiographic and cardiac catheterization data in this entity which reveal the abnormal hemodynamics and the compensatory mechanisms present. The pathologic findings in this case have been reported.[2] Our observations indicate that this entity may be diagnosed during life. The hemodynamic data are in accord with those of experimental studies[3-7] which demonstrate persistence of the pumping activity of the right ventricle even after extensive to nearly total destruction of its myocardium.

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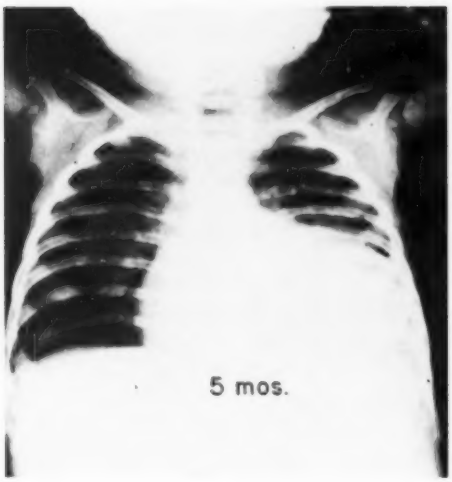
CASE PRESENTATION

K. K., a 5-month-old, fairly developed but undernourished white male infant, was admitted to the cardiology ward of the Cook County Children's Hospital with a history of occasional vomiting spells, insufficient weight gain, and bouts of tachypnea not related to feedings or to any specific event for the past 2 months. He was the product of a normal gestation and spontaneous delivery and his birth weight was 6 pounds, 7 ounces. The mother was not ill during pregnancy, nor did she have any history of miscarriage.

Physical examination revealed a noncyanotic, afebrile infant, in no distress, weighing 10 pounds, 14 ounces. There was no clubbing of the fingers or toes. The respiratory rate was 36 per minute, and the pulse rate was 140 per minute. The radial



A

C

B

Fig. 1. Chest roentgenograms in posteroanterior (*A*), right anterior oblique (*B*), and left anterior oblique (*C*) views. Note marked cardiac enlargement and normal to diminished pulmonary vascular markings. Arrows in the left anterior oblique view indicate the posterior border of the heart.

and femoral pulsations were normal; the blood pressure in the right arm was 70/58 and in the left leg was 78/60. The neck veins were not distended. Examination of the head and neck gave essentially normal findings. A few moist râles were present at the left lung base posteriorly. The cardiac apex was at the sixth left intercostal space at the anterior axillary line. No parasternal heave or precordial bulge was noted. The first, second, and third heart sounds were of normal or somewhat diminished intensity. The second sound appeared single and was heard best over the pulmonic area. A Grade I, soft and short systolic murmur was present at the midprecordium and base. The liver was soft and enlarged, with its edge extending 3 fingerbreadths below the right costal margin. The spleen was not palpable. There was no edema of the extremities.

The hemogram revealed hemoglobin 89 per cent, red blood cells 4.6 million, white blood cells 13,900 with normal differential count. Fluoroscopic and roentgenologic examinations of the chest in the posteroanterior and in the right and left anterior oblique views revealed marked cardiac enlargement and what appeared to be normal or diminished pulmonary vascular markings (Fig. 1). A 15 lead electrocardiogram showed regular sinus rhythm, a rate of 136 per minute, a frontal QRS axis of −110 degrees, a P-R interval of 0.14 second and a QRS interval of 0.05 second. The P waves were tall and peaked in Leads II, aVF, V_2 and V_3, and were biphasic ove

Leads V_{4R} through V_1. In the right precordial tracings, qR complexes with maximal R waves of 4.5 mm. were accompanied by isoelectric T waves. In V_4 through V_7, qRs complexes were present, accompanied by negative T waves (Fig. 2). This tracing and two other similar tracings were interpreted to indicate right atrial hypertrophy, left ventricular hypertrophy, and probable right ventricular hypertrophy.

The clinical impressions were Ebstein's anomaly, congenital endocardial fibroelastosis, anomalous origin of the left coronary artery, or glycogen storage disease of the heart. Two days after admission an anteroposterior peripheral venous angiocardiogram was performed with the use of a Fairchild roll-film serial changer. A total of 24 exposures taken at ½ second intervals were obtained. The angiocardiogram demonstrated failure of the contrast substance to disappear completely from the right heart chambers and a marked delay in the opacification of the left heart chambers starting 8 seconds after injection. The right atrium and right ventricle were enormously dilated while the main pulmonary artery and branches appeared normal or small. Fig. 3 demonstrates these findings. At 1 second (*A*) and 1½ seconds (*B*), the contrast substance has completely opacified the right atrium but not the right ventricle. The atrioventricular orifice appears to be normally located. At 2 seconds (*C*), the right ventricle is well visualized. There are no identifiable trabeculae and the wall of this chamber is unusually thin. The opened tricuspid valves (arrows) and the relatively smaller right atrial chambers indicate right ventricular diastole. At 5 seconds (*D*), the hepatic veins, right chambers, and pulmonary arteries are still well visualized. The right atrium is markedly dilated and the right ventricle remains virtually unchanged in size. At 8 seconds (*E*), the left chambers and aorta start to be opacified. The hepatic veins, right chambers, and pulmonary arteries are still well seen and this persists even until the end of the procedure at 12 seconds (*F*). The left ventricle is dilated but appears relatively smaller than the right ventricle.

Right heart catheterization was done with the infant under intravenous Pentothal anesthesia with a No. 6 Fr. catheter introduced into the right saphenous vein. No arrhythmias were encountered in the procedure. The left atrium and pulmonary vein were entered through a patent foramen ovale. The catheter outlined the huge right atrial and right ventricular chambers and the normal location of the tricuspid ring. There was no evidence of an intracardiac shunt and the cardiac output was small. The right ventricular and pulmonary artery pressure curves revealed presystolic elevation with identical magnitude and temporal relationship as the tall right atrial "a" waves (Fig. 4). The catheterization data are summarized in Table I.

With digitalis, diuretics, and oxygen the size of the liver regressed although the cardiac enlargement persisted. The glycogen content of a muscle biopsy was within normal limits. The infant was discharged 3 weeks later with the diagnosis of congenital endocardial fibroelastosis or myocarditis.

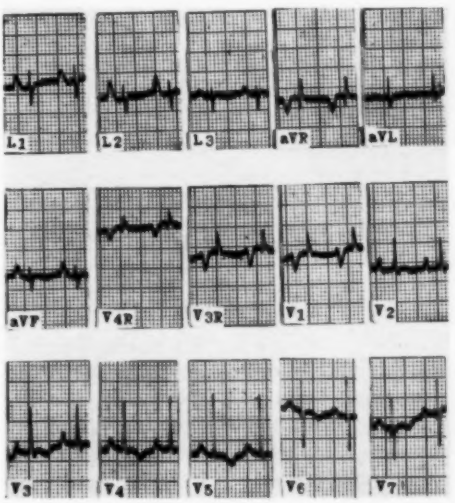
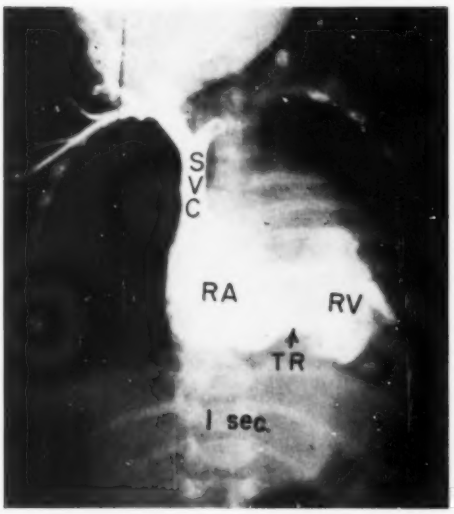
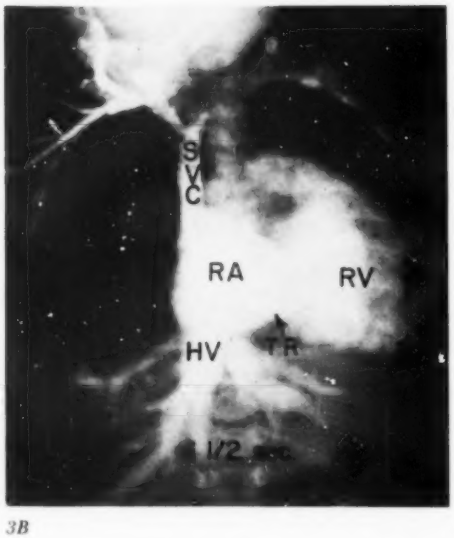


Fig. 2. Fifteen-lead electrocardiogram. Note small qR complexes in V_{4R} through V_1, tall and peaked P waves in L_2, aVF and V_2, and negative T waves in V_3 through V_6.



3A



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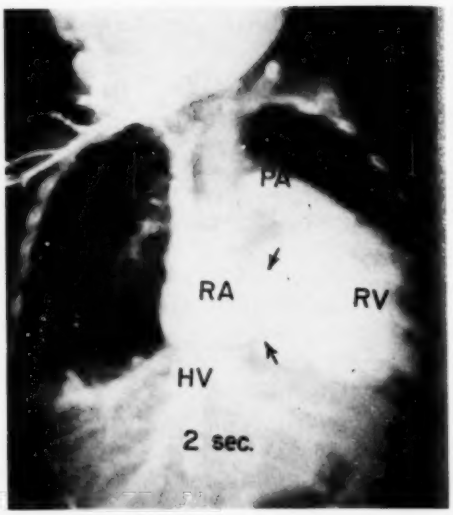


3C

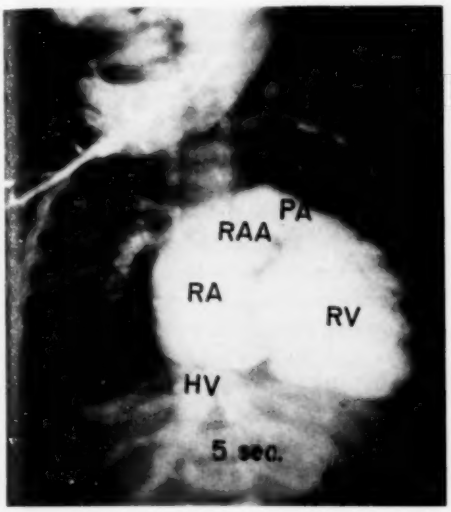
Fig. 3. Anteroposterior angiocardiograms taken at 2 frames per second. Note normal location of the tricuspid ring at 1 second (*A*) and 1½ second (*B*) frames. At 2 seconds (*C*), the opened tricuspid valves are visualized (arrows). Note the marked dilatation of the right atrium and right ventricle, the small or normal-sized pulmonary arteries, the unusual thinness of the right ventric-

He was seen regularly in the cardiac clinic and was readmitted at the age of 8 months for an upper respiratory infection. The clinical findings including the chest roentgenograms and electrocardiogram were unchanged. At the age of 1 year he was rehospitalized because of severe congestive heart failure. Marked cardiomegaly was accompanied by diastolic gallop rhythm, faint heart tones, and a Grade I short, soft systolic murmur at the midprecordium. The chest roentgenograms revealed further increase in the heart size while the electrocardiogram remained unchanged. He died on the same day.

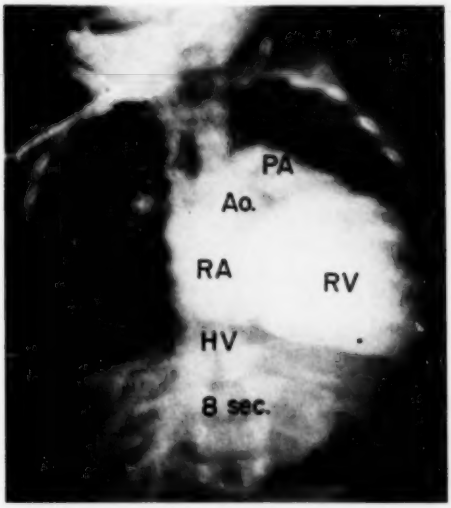
A brief description of the findings at autopsy* follows:

The heart was markedly dilated, particularly the right atrium, right ventricle, and left ventricle. The systemic and pulmonary veins and the great vessels were normally situated. Except for an area just below the tricuspid ring which measured 5 mm. in thickness, the wall of the right ventricle was 2 mm. thick and consisted chiefly of thickened milky white endocardium and epicardium. The papillary muscles and trabeculae were paper thin and consisted only of fibrous connective tissue except in a few areas where sparse muscle fibers were noted. The crista supraventricularis was

*The necropsy studies were performed by Dr. Paul E Szanto, Head, Department of Pathology, and associates.

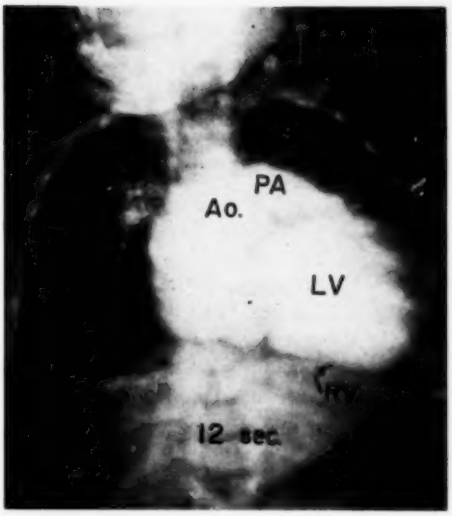


3D



3E

ular wall, and absence of trabeculae. At 12 seconds (*F*) the left ventricle is well outlined and, although dilated, it is relatively smaller than the right ventricle. *SVC,* superior vena cava; *HV,* hepatic veins; *RA,* right atrium; *TR,* tricuspid ring; *RV,* right ventricle; *PA,* main pulmonary artery; *LV,* left ventricle; *Ao,* ascending aorta. (For discussion see text.)



3F

hypoplastic. The right atrium was markedly dilated; its wall was 2 mm. thick and the appendage was 3 mm. thick. The endocardium was similarly thickened. The foramen ovale was patent to a probe. The left atrium was normal in size. The left ventricle was hypertrophied and dilated, its wall measuring 3 to 7 mm. in thickness. The endocardium was also thickened similarly to that in the right chambers. The ductus arteriosus was practically closed. The atrioventricular and semilunar valves were normal. The final anatomic diagnosis was: marked hypoplasia of the myocardium of the right ventricle; fibroelastosis of the right ventricle, right atrium, and left ventricle; and probe patency of the foramen ovale.

DISCUSSION

The pathologic findings in the present case closely resemble those reported by Uhl.[1] Our case differed only in the presence of fibroelastosis in the left atrium and left ventricle which was not present in his case. The etiology of this anomaly is not known. It is assumed to be due to a developmental arrest involving the anlage of the future myocardium of the right ventricle.[1] The fibroelastic proliferation of the endocardium of the right heart chambers probably represents an exaggerated tissue response of the endocardium to the great tensions to which it is subjected.[8, 9]

The pressure pulse tracings in our case demonstrated that, in spite of a nearly total absence of the myocardium of the right ventricle, systolic contraction of this chamber still occurred. This observation is in keeping with those of experimental studies[3-7] which demonstrated that acute extensive destruction of the right ventricular myocardium of approximately 70 per cent to nearly 100 per cent still results in adequate pulmonary blood flow at rest. Careful scrutiny of our pressure pulse tracings, however, reveals that the greater portion of the pressure rise in the right ventricle and in the pulmonary artery occurs during presystole and that this rise has identical magnitude and temporal relationship with the augmented "a" wave in the right atrial tracing (Fig. 4). We have not encountered these abnormal pressure tracings previously nor are we aware of reports demonstrating identical curves. The pressure tracings in Ebstein's anomaly may manifest elevated end-diastolic waves in the pressure curve of the right ventricle[10, 11] and pulmonary artery[11, 12] with identical temporal relations as the right atrial "a" wave, but in none of the reported tracings was the end-diastolic pressure as high or the differences between the systolic pressures of the right ventricle and the right atrium so small. This implies that in these cases of Ebstein's anomaly forceful right ventricular contraction still occurs. In contrast, the elevated diastolic and relatively low systolic pressures in the right ventricle in our case indicate profound myocardial failure, this chamber functioning mostly as a large reservoir for venous blood. It is a constantly overloaded chamber and not only does isometric contraction fail to occur but the initial pulmonary blood flow precedes the electrical and mechanical systole of the right ventricle. This is obviously due to right atrial contraction. The later propulsion of blood into the pulmonary arterial system is, however, due to right ventricular contraction. The elevated pulmonary venous and left atrial pressures are due to left ventricular dysfunction accompanying the endocardial fibroelastosis. This accounts for the elevated total pulmonary resistance (Table I) and the increased work load of the right heart chambers. The high systemic arteriovenous oxygen difference is due to the marked congestive heart failure.

The pathophysiology just discussed explains the clinical features. The marked cardiac enlargement was not accompanied by a precordial bulge or a left lower parasternal lift and by evidences of pulmonary hypertension or tricuspid regurgitation. The conspicuous absence of these accessory findings is due to poor right ventricular contraction. The marked enlargement of the right heart chambers and the diminished pulmonary blood flow in the chest x-rays are explained similarly. The electrocardiographic evidences of right atrial hypertrophy and left ventricular hypertrophy (Fig. 2) need no further explanation. The small qR complexes and isoelectric T waves over V_{4R} through V_1 were incorrectly interpreted by us as suggestive of right ventricular hypertrophy. In retrospect we now believe that the initial r wave was isoelectric and that the qR complex in the right

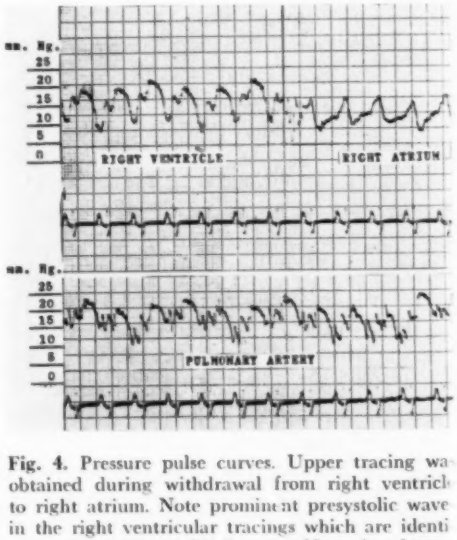


Fig. 4. Pressure pulse curves. Upper tracing was obtained during withdrawal from right ventricle to right atrium. Note prominent presystolic waves in the right ventricular tracings which are identical to the right atrial "a" waves. Note also absence of any significant "v" waves in the right atrial tracing. Lower tracing is a pulmonary artery tracing demonstrating similar presystolic waves.

Table I. Cardiac catheterization data

Blood samples	O_2 content (vol. %)
Inferior vena cava	3.95
Superior vena cava	2.65
Right atrium, upper	4.55
Right atrium, lower	4.37
Right ventricle	5.14
Main pulmonary artery	4.43
Left atrium (or pulmonary vein)	13.03 (91%)
O_2 Capacity	14.31
Intravascular pressures (mm. Hg)	
Right atrium	
"a" wave	14
"v" wave	10
Mean	(11)
Right ventricle	
Systole	20
Diastole, early	8
Diastole, end	15
Pulmonary artery	
Systole	21
Diastole, early	8
Diastole, end	16
Mean	(15)
Pulmonary vein (mean)	(16)
Left atrium (mean)	(16)
Cardiac output	1.7 L./min./M.^{2}
Calculated pulmonary resistance:	
Total	706 dynes sec. cm.$^{-5}$/M.^{2}
Arteriolar	46 dynes sec. cm.$^{-5}$/M.^{2}

precordium was actually an rsR′ complex which does not indicate right ventricular hypertrophy.

The most important angiocardiographic features which appear to be diagnostic of this anomaly are: the demonstration of a normally located tricuspid ring, a finding not encountered in Ebstein's anomaly, the unusual thinness and huge dilatation of the right ventricle, and the conspicuous absence of its normal trabeculae (Fig. 3).

Since the basic abnormality appears to be the insufficient pumping mechanism of the right ventricle, the work load of this chamber may be considerably improved by short-circuiting the systemic venous return directly to the pulmonary circulation. Successful permanent circulatory bypass of the right heart chambers has been performed experimentally[13-16] and clinically.[17-19] We believe that a partial venous bypass of the right heart by means of a superior vena cava—right pulmonary artery anastomosis should be attempted as a palliative measure.

SUMMARY

The previously unreported angiocardiographic and hemodynamic findings in a proved case of congenital aplasia or marked hypoplasia of the myocardium of the right ventricle are presented. The clinical picture consisted of progressive heart failure in infancy, marked cardiomegaly, feeble triple heart tones, no significant murmur, and absence of clinical evidences of right ventricular hypertrophy, pulmonary hypertension, or tricuspid regurgitation. The chest roentgenograms demonstrated marked cardiac enlargement with normal or diminished pulmonary vascular markings. The electrocardiogram showed right atrial hypertrophy and left ventricular hypertrophy. Cardiac catheterization revealed normal systolic pressures and markedly elevated presystolic waves in the right ventricular and pulmonary arterial pressure curves which were identical with the right atrial "a" waves. We have not encountered nor have we seen any reports in the literature showing identical curves. The angiocardiograms demonstrated enlarged right heart chambers, diminished pulmonary blood flow, unusual thinness of the right ventricular wall, and conspicuous absence of it trabeculae. We believe that the correct diagnosis may be derived from the clinical, cardiac catheterization, and angiocardiographic findings. It is suggested that a superior vena cava–right pulmonary artery anastomosis be performed for palliative treatment of this anomaly.

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Programing for children with a neurological deficit

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A CHILD born with a neurological insult or acquiring it early presents a real medical challenge. Many physicians unfortunately cannot see the *child* for the handicap. The pediatrician's knowledge of children is essential for the proper programing and he should assume this responsibility.

The problem of the child with a neurological deficit involves not only many disciplines but presents many dimensions, the latter depending on the child's original endowment, the location and extent of the injury, and the environment into which he is born. Unlike adults who suffer neurological insult, children have no past experience upon which to build: How does the child interpret the world if he has no vision; if his hearing is impaired; if he cannot express himself verbally; if he cannot remember two or three consecutive requests; if the symbols meaningful to us all look alike to him?

Those of us who work intimately with these children know that many of them have strong motivation, a sense of humor, a need for gratification, acceptance, praise, and love. They have a right to their little lives. They too are human beings.

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Programing for them is not difficult. Our plan has evolved over a period of nine years and the type of organization we feel practical will be described briefly.

ORGANIZATION

Staff.

Medical. A pediatrician should be in charge of the program. He should have available for consultation or for therapy when indicated an orthopedist, a neurologist, a neurosurgeon, an ophthalmologist, an otologist, and a psychiatrist. Not every child needs all the consultants and only a few children need continued treatment by specialists. At times long-term orthopedic care is indicated and frequently the services of an ophthalmologist are necessary.

Ancillary. A social worker is indispensable. The services of a psychologist, audiologist, speech therapist, and teacher are necessary. The physical therapist and occupational therapist are a part of the treatment team.

Referral. The services should be available to all patients regardless of financial status. In order to avoid interference in any way with the private practice of medicine we have limited our work to the problems associated with the handicap, leaving all other care such as immunizations, sick calls, and routine office work to the private phy-

sician or the clinic in which the family is registered. Referral therefore is by a doctor or clinic only.

Finances. Our work began as a program for the preschool cerebral palsy child under the local Cerebral Palsy Association. The United Cerebral Palsy Association has paid for ancillary personnel. The doctors have volunteered their services in a manner somewhat similar to that of the Tumor Board organization.

Two other sources of income have been added. In 1959 the Crippled Children Services certified the clinic for neurological diagnostic study on its program.

The Little Jim Club of Children's Hospital and other private organizations and individuals have donated funds from time to time. These have made it possible for us to see children with neurological problems not eligible under the Crippled Children Services or Cerebral Palsy.

A fee for private services has been considered but has not yet been instituted.

Admission routine. The method followed upon referral may vary somewhat but in general a social history is first obtained and as much past information as possible gathered. The child is then seen by the pediatrician and a medical evaluation made, including necessary laboratory work.

The medical and ancillary consultations as indicated are then set up. When all of these have been completed a staff conference is held which accomplishes the following:

1. It summarizes the findings of the group, thereby establishing a preliminary diagnosis and an estimate of the child's ability.

2. Based upon the above conclusions, a plan of procedure is agreed upon. This includes therapy and/or education.

3. The appropriate time for the next evaluation is set.

4. The person is selected who is to interpret the findings and the plan to the parents. This is usually the pediatrician in conjunction with the social worker, together or separately. In some instances it may be left entirely to the private physician who referred the patient and who may have participated in the conference.

THERAPY

The major part of our therapy program at present is concerned with the cerebral palsy preschool child. For this we have a therapeutic nursery school five mornings a week. The children come one, two, three, or five mornings, depending on their age, the extent of involvement, and several other factors. Infants are usually seen once a week. Older, severely handicapped children are given individual therapy in the afternoons.

Therapy during infancy (as the parents themselves express it after the first several months) is more for the parents than the child. Parental adjustment to the information that a child is handicapped takes from four to six months and sometimes longer. Regular attendance provides opportunity to talk to other parents, to the social worker, to the teacher, therapists, and physicians, all of which helps the mother resolve her anxiety. Our observations are very similar to those of Knudson and Natterson,[1] as reported recently. Unlike their experiences with the parents of fatally ill children, a few parents seem unable to adjust to the presence of a handicapped child in the family. There are instances where the irresistible force seems to meet the immovable object. The great majority of parents, however, are grateful for the help they receive and assume their responsibility in an exemplary manner.

It is not correct, however, to think that therapy is solely for the parents. Those of us who have watched these children grow and develop in a situation where they participate as nearly as possible in experiences of normal children are convinced that this is good therapy. These children are accepted. Many have tremendous determination and drive. They have a sense of humor. They proceed to new experiences with confidence. Again, our experiences parallel those of Knudson and Natterson.[1] The very young child needs tremendous support from the mother. The school child from 6 to 10 goes

through a critical experience in the area of learning. If he can keep up with his peers at this period, in other words, if he can learn to read and write and figure, the greatest battle is won. From 10 years on the child becomes more objective. He looks at his handicap and handles his situations with it in a more adult manner. It is also easier then to talk to the child himself and to get his cooperation. Our staff feels that the first 8 to 10 years are exceedingly important and of these years the first 5 or 6 are the most important. The aim in our center is not to provide a substitute for a school program. The community has facilities for the education of children with various types of handicaps. Most of the special schools or classes admit children at 3 years but in many instances the children are not ready for public school until 3½ or 4, or even later. It is our aim to prepare the children for this later school experience.

Weekly staff conferences are held at which the readiness of the child to move to the next activity is discussed. Even after transfer the child continues to return to the medical clinic for follow-up. The social worker and teacher are present at this clinic and assist in solution of problems that may have arisen.

In addition to this nursery school program, individual evaluations are made of other children. This work is done in the afternoons, primarily by the nursery school teacher and the psychologist. This type of evaluation has been made of selected blind, deaf, and hyperkinetic children who, beyond the usual age, have not adapted to the public school facilities designed for them. Other children between the age of 5 and 10 years, particularly, have been placed in occupational therapy to help them to conform sufficiently to be placed in public classes.

The pediatric clinic is held twice weekly, not only for new patients but for return visits between the major evaluations and for continued longitudinal study of the children who are registered with us.

Location of program. It is our contention that a program, such as is described here, belongs in a hospital setting. In a recently completed survey of rehabilitation services in San Francisco, Dr. Irving Babow[2] strongly recommends hospital location. It need not be in connection with a medical school; often it is better located in another hospital. It is a community service, primarily. Medical schools must devote a great deal of time to education which may mean that the number of patients must be limited. Furthermore, many communities do not have a medical school. This health program is designed primarily to meet community needs. Education and research, although important, are secondary.

If located in a public health building, the service is often forgotten by private physicians. If it is in a separate institution, it lacks adequate medical participation. Location in schools has so many serious drawbacks it should not even be considered.

The close daily cooperative efforts of the educator, psychologist, social worker, and pediatrician and the frequent discussions with other medical consultants have enhanced the staff's understanding of the learning processes in children with a deficit. This knowledge is of value in dealing with normal children. Variations occur bordering on the abnormal in many children. The work has given us insight into frustrations, rebellion, aggression, and withdrawal. The effect of parental attitudes on the children is often very obvious.

SUMMARY

A program designed to help the child with a neurological handicap has been described. It is suggested that such programs be located in hospitals and that pediatricians assume the major responsibility for this type of habilitation.

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TROPICAL PEDIATRICS

Kwashiorkor in Cape Town: the background of patients and their progress after discharge

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KWASHIORKOR is a disease resulting from a deficiency of protein-rich food relative to starchy sources of calories. Further study of the factors contributing to this deficiency and the long-term effects of it seems to be necessary, the former from the preventive health angle, the latter from the clinical.[1] Studies in Durban,[2] Coonoor,[3] and Kampala[4] have illuminated the background of malnutrition in those areas. Where follow-up studies have been done,[5-7] the difficulty of maintaining contact over a period of years has been considerable and there is reason to suspect that the untraceable cases may have been those that lived under the most unfavorable conditions with the greatest likelihood of relapse. The current project is an attempt to combine an inquiry into the contributory causes of the disease with a prospective follow-up study of a consecutive series of fully investigated, acute, hospitalized cases. Interim results of this inquiry are presented here.

From the Clinical Nutrition Research Unit of the Council for Scientific and Industrial Research in the Department of Medicine, University of Cape Town.

This study was financed by the Council for Scientific and Industrial Research, the Staff Research Fund of the University of Cape Town, and the Williams Waterman Fund for the Combat of Dietary Diseases, New York.

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THE SOCIOCULTURAL FACTORS UNDERLYING THE SYNDROME

Environment and population. The patients' homes were within the urban or periurban area of Cape Town, a busy seaport which has had a rapid growth of industry since World War II. To meet the resulting need for a larger labor force there has been a migration of Xhosa-speaking Bantu manual workers mainly from the rural Eastern areas of the country. Thus four distinct racial groups are represented, and in the following numerical order: Cape Colored and Malay,[8] European (Caucasian), African (Bantu), and Asian.

Material used. Results are based on the first 150 completed medical-social questionnaires on children with kwashiorkor admitted to the Groote Schuur and Red Cross

War Memorial Children's Hospitals since November, 1958. Of these 119 were Cape Colored, 25 African, 5 Asian, and 1 European. There were 93 males and 57 females. The criteria for diagnosis conformed with those of Brock and associates.[9] The control group was composed of 150 children of families in which one member had been hospitalized with kwashiorkor, but in which no others had a history of the disease and all had passed the age at which their sibling had become ill. Of these, 127 were Cape Colored and 23 were African children. There were 71 males and 79 females.

Method. On the child's admission the mother was interviewed and a questionnaire was completed relating to the present illness, the past history, and the home situation including family, finances, and environment. Great importance was attached to the technique of the interview and the establishment of a relationship within which the mother would feel as free as possible to describe the situation as it appeared to her. The plans for follow-up were explained to her and she was taken home by car in order that the situation might be personally assessed and that the place might be found again. The interviews and visits were conducted by the same person throughout the series. At this or a later visit the weights and heights of siblings, relatives, and other playmates of the patient were often recorded in order to assess the growth attainment of the population at risk.

Results.

Race, sex, and age distribution. The races mainly affected were the Cape Colored and African, in numbers conforming with the relative sizes of these groups. As elsewhere[4] males were more often affected than females, forming 62 per cent of the kwashiorkor cases and 47 per cent of the controls. The peak age period for admission was from 10 to 18 months of age. This was an early age compared with the consolidated observations of Trowell, Davies, and Dean[10] but resembled the findings of Kahn and associates[11] in Johannesburg and conformed with the prognostications of Trowell and Jelliffe[12] and of Symonds[13] as to what might happen in rapidly industrializing communities.

Factors related to protein deficiency.

SHORT DURATION OF BREAST FEEDING. Table I shows the earlier age at weaning of the hospital cases of kwashiorkor than of babies normally attending Cape Town Welfare Clinics,[14] a finding that merits attention. For the purposes of comparison, figures from Welbourn's Clinic Series[15] are included, showing a greatly superior achievement in breast feeding at Kampala although it reports a decrease there, too, even over a period of 5 years.

The Cape Town hospital group is composed of all races but is mainly Cape Colored. In order to judge whether the African mothers, commonly considered to secrete more milk than the Cape Colored, had also failed in this respect, data for them were then taken separately; the results are given in parentheses.

There is reason to believe that the mothers who attend welfare clinics include the more responsible members of their socioeconomic class and are, to that extent, a somewhat

Table I. Age at weaning

	Kampala Welfare Clinic		*Cape Town Welfare Clinic*		*Cape Town Hospital*			
					African and Cape Colored		*African*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
No. of cases	285		200		146		(23)	
Completely bottle-fed by 1 month	4	1.4	—		44	30	(8)	(35)
Completely bottle-fed by 3 months	—		25	12.4	78	53	(13)	(56.5)
Completely bottle-fed by 6 months	12	4	45	22.5	98	67	(15)	(65)

selected group. Comparison was, therefore, also made of the breast-feeding records of patients with those of children in the control group aforementioned, i.e., siblings of hospitalized cases of kwashiorkor, and the results are listed in Table II. They demonstrate that a greater number who developed kwashiorkor had received little if any breast feeding and a smaller number had received breast feeding after 6 months of age.

An attempt was made to discover why weaning by 3 months had occurred in 53 per cent of the cases of kwashiorkor and the results are given in Table III.

The explanations "no milk" and "weaned themselves" are sometimes a reflection of poor lactation, and in other instances of the random interspersion of breast feeding with bottles of sweetened water, tea, or diluted milk through a well-used nipple that demands no effort. The truth is, probably, usually a combination of both of these.

INADEQUATE MILK AT ONSET OF SYMPTOMS. When the history of a patient was taken on admission, an estimate was made of the amount of milk given daily during the previous 2 to 3 months or longer. It was usually clear on this evidence alone that the child was in danger of developing kwashiorkor since the rest of the diet was likely to be poor in protein. Suspicions were aroused, however, that in many instances the milk intake had not differed greatly from that of the child's siblings at a similar age. Table IV indicates that, in a large number of instances, this was indeed the case. Black tea or coffee are the accepted drinks from about 9 months of age and often earlier and this is partly why it is so difficult to convince the mother that the patient's diet caused his illness.

Table II. Age at weaning of patients and patients' siblings

	Patients		*Siblings*	
	No.	*%*	*No.*	*%*
No. of cases	146		146	
Weaned at under 1 to 3 months	78	53	57	39
Breast-fed longer than 6 months	48	33	80	55

Table III. Reasons for weaning by 3 months of age in children who developed kwashiorkor

	No.		*%*	
Total No. of cases	78			
Mother went to work	5		6	
Mother ill	4		5	
Baby ill or premature	2		2.5	
Misguided advice	5		6	
Sore nipples	4		5	
"Weaned themselves"	10	58	12.8	74.3
"No milk"	48		61.5	

FOOD NORMALLY GIVEN AT ABOUT 1 YEAR. It is possible that in the case of the controls the deficit of protein from milk may have been made good by that derived from other protein-rich foods which vary in amount according to the income available. The first solid food given at about 6 months is often the so-called gem-squash (var. *Cucurbita pepo* L.), a watery marrow of minimal caloric value, or maize or oats porridge, frequently without milk. Later the diet settles into a monotonous routine including porridge, root vegetables, squash or pumpkin, and bread (white or brown) with variable amounts of meat and fish. There is a feeling that meat and dried beans are "too strong" for a child and should be avoided. Quite often the mothers relate that the prekwashiorkor child was very fond of fish or of meat when he could get it; others have observed shortly before the acute stage, a craving for salty foods and speak of the child's only sucking the juice from the meat. Eggs are seldom given, not because of any taboo, but because of the cost. Hardly any families grow their own vegetables so that the diet depends on the money income except in the occasional case where a member of the household is employed on a fishing boat and can bring fish home.

POOR GROWTH OF THE POPULATION AT RISK. From the foregoing it can be seen that the control group of weaned children, even if they were drinking only black tea, might possibly have escaped kwashiorkor by having been breast-fed longer and more adequately and avoiding infection for a longer

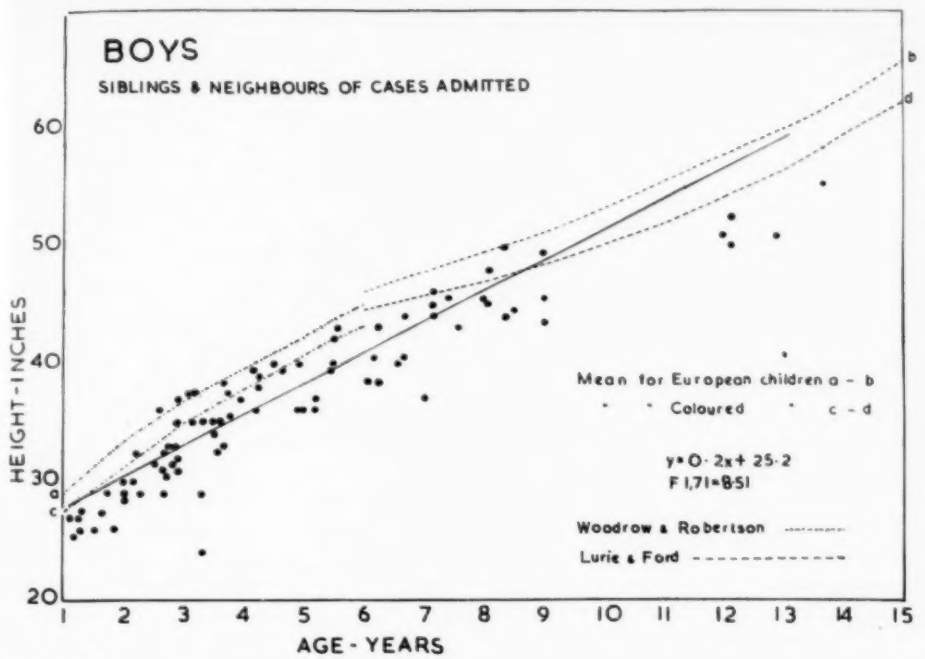

Fig. 1. Boys' annual increase in height (inches).

time than the others, as well as by subsequently getting a diet that included more adequate quantities of protein foodstuffs. Nevertheless, the growth rate of the child population at risk shows, as is to be expected, the retardation which is one of the early manifestations of protein deficiency.[16, 17] In Figs. 1 to 4 the weights and heights of siblings and playmates of Cape Colored patients, recorded for this purpose, are plotted against the local mean curves,[18, 19] demonstrating again that the extent of malnutrition in a group cannot be estimated by manifest deficiency disease only.[20]

Factors related to infection. One of the striking features of the surroundings and homes of this group is the poor hygiene. Gopolan[21] in India has suggested that improvement in this alone might effect great improvement, and Robertson and associates[22] have pointed out that the incidence of gastroenteritis, a frequent precursor of kwashiorkor, is far lower in housing estates than in slums where the hazards of bottle feeding at an early age are very considerable. The recorded incidence of diarrhea among the control series was 15.3 per cent and among the kwashiorkor series, 73 per cent. This is in keeping with previous reports on the high incidence of diarrhea in kwashiorkor[23] and with metabolic data on intestinal absorption.[24] In about a quarter of the Cape Town cases the diarrhea appears to be infective in origin but it has been suggested that a protein-deficient diet itself,[17] the suppression of digestive enzymes,[25, 26] the atrophy of the intestinal mucosa in a malnourished child,[27, 28] or the overgrowth of intestinal bacterial flora[29] may also play a part. A recent article[22] outlines the relation of malnutrition to gastroenteritis in the Cape, and kwashiorkor may be considered as part of the same continuous process among children who have survived the period of infancy.

Apart from diarrhea there was, in 8.5 per cent of the cases of kwashiorkor, a history of measles from which the child had never fully recovered, and in 6 per cent of the

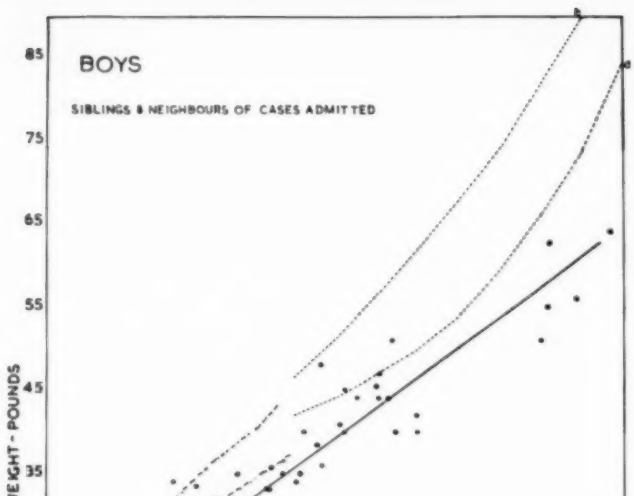

Fig. 2. Boys' annual increase in weight (pounds).

cases the child had pneumonia on admission. Whooping cough and chickenpox had also occurred in several cases, and tuberculosis was present in some but the extent to which it precipitates kwashiorkor in the Cape Town area cannot be judged, as the tendency was to refer the child elsewhere if tuberculosis had been diagnosed on x-ray when he was an outpatient.

Social factors underlying both malnutrition and infection.

IGNORANCE. The importance of this factor is widely recognized but difficult to assess. Judged by standards of school education it was found that 16 per cent of the mothers of the sick children had had no schooling and a further 51 per cent had gone no further than the standard normally attained by a European child of about 10 years. In a modern urban community with the need to budget on a small income and to resist plausible sales talk the uneducated adult is at a disadvantage; but other factors, like the mother's own background, upbringing, and general capacity are probably more important.[30] It was clear that, in the group studied, knowledge of correct feeding had seldom been achieved although the mothers had managed to learn incorrect ideas that were not indigenous, e.g., the child must be sure to get his squash and carrots; glucose, although expensive, is very good for a child; black tea should be given as long as there is any diarrhea, with the natural deduction that milk gives diarrhea and black tea prevents it. The mother's use of the resources of the community, particularly the child welfare center, was considered a fair indication of efficiency. Table V indicates the extent to which these clinics were used for the children who later developed kwashiorkor and for the siblings who did not.

The similarity in numbers of those in both groups who never attended is to be expected since the mothers of the controls came from the same series as the mothers of the pa-

tients. The difference in health between those who did and did not attend is the more striking and a tribute to the success of the clinics when use is made of them. The group with irregular attendance may, for practical purposes, be grouped with non-attenders, as in many cases the children were taken only when sick and not for preventive health reasons. Here, as among other undeveloped peoples, the concept of well-baby clinics is not easily grasped.[31]

A minor indication of maternal ignorance is the extent (57 per cent) to which local remedies are still used before medical advice is sought. By far the most popular of these for kwashiorkor is the local "wilde als" (*Artemisia afra* Jacq.).[32] The aromatic leaves are packed onto the abdomen and an infusion of them is given to the patient to drink. Considerable use is still made of a variety of "Dutch remedies" available at shops, and, in the houses of the poor, there is usually a selection of little bottles of this or that kind of patent medicine or "strengthening mixture." Some use is still made of witch doctors by Africans and there is evidence among some of the African and Cape Colored patients of fixed and fearful belief in the influence of ill-wishers and evil spirits, of "Malay tricks," and "tokoloshi." It was not felt in this survey, however, that these beliefs had delayed the seeking of medical advice in the majority of cases. There seems to be no great cultural barrier to systematic health education among the Cape Town population.

POOR HOUSING AND SLUM CONDITIONS. The homes of the patients were considered in over 90 per cent of the cases to be unsatisfactory from the point of view of hygiene, although many showed evidence of effort on the part of the parents to make them agreeable. Some were frankly hovels, others were homemade shacks, and yet others were rooms rented in brick houses which often seemed darker and more sordid than the rest. Some cases of kwashiorkor did also occur on the new housing estates where costs of rent and transport reduce the amount of income available for food.

POVERTY. Table VI indicates the economic status of the household from which patients

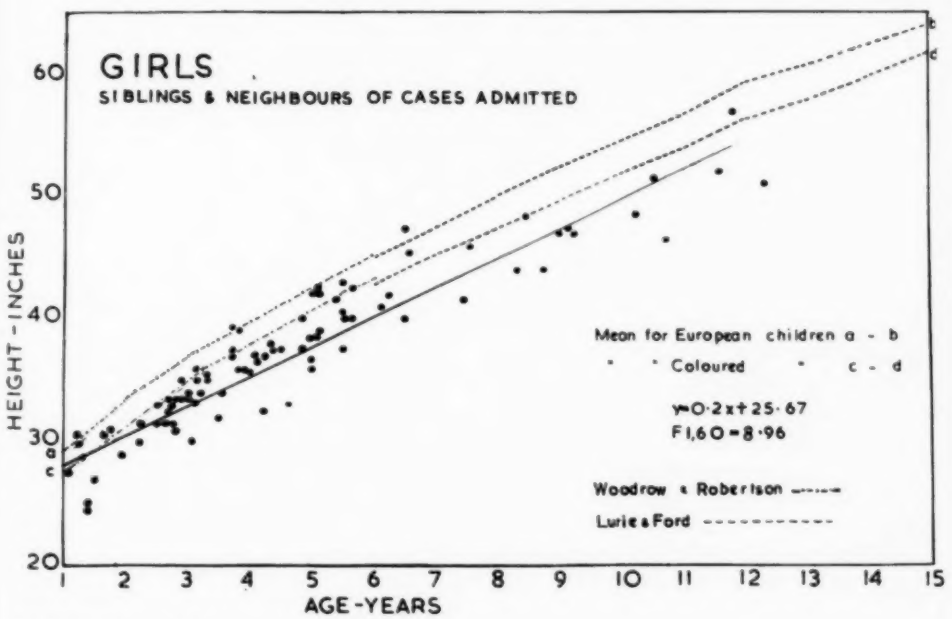

Fig. 3. Girls' annual increase in height (inches).

with kwashiorkor came, compared with the figure quoted by Suckling[6] for the general population of the area in 1953. The Poverty Datum Line[32] is the income required to obtain a bare minimum level of subsistence and does not indicate a "human" standard of living. The Effective Minimum Standard is at least one and a half times as great as the Poverty Datum level and allows for slightly more than the barest necessities. The very low economic standard in 82 per cent of patients' homes is identical with the figure reported by Suckling. In 81 cases among the sibling controls, information was available in regard to the household income when these children were young. In Table VII the results are compared with those of households where kwashiorkor occurred. Allowance must be made for inaccurate memories and other sources of error, but the data seem to indicate the progressive inadequacy of current wage rates as families grow and the increasing risk of nutritional disease in families subsisting on marginal incomes.

UNEMPLOYMENT OF FATHERS. Table VIII compares the employment history of the breadwinners in the two groups and shows them to be similar except for the more frequent occurrence of kwashiorkor when the father's work was irregular or casual. In the families in which a child developed kwashiorkor, however, 42 per cent of the fathers had been unemployed for 1 month or more in the 6 months preceding the child's admission, demonstrating again the marginal nature of family subsistence and the sensitivity of the toddler to any resulting change in the barely adequate protein-calorie ratio of his diet. Even 1 week's loss of wages can involve such families in debt from which it takes long to recover.

Table IV. Milk consumption of patients and controls

	Patients at onset of disease		*Siblings at approximately the same age*	
	No.	*%*	*No.*	*%*
No. of cases	138		134	
Getting some milk as a drink	5	3.6	21	15.6
Getting milk mixed with other drink	41	29.6	27	20.1
No milk or negligible amount	92	66.6	86	64.1

Table V. Attendance at child welfare clinics by patients and siblings

	Patients			*Siblings*		
	No.	*%*		*No.*	*%*	
No. of cases	143			130		
Regular attendance for the time allowed	23	16		40	31	
Irregular	51	36	84	26	20	69
No attendance	69	48		64	49	

OTHER FEATURES OF SOCIAL DISORGANIZATION. Over 40 per cent of the mothers in both series were engaged to some extent in work, mainly of a domestic nature, outside the home. Although very significant in the incidence of gastroenteritis in the infant group,[22] this appears to be less so in the kwashiorkor age group, presumably because the older child can more safely be left in the care of a sibling or an adult.

The figure for illegitimacy among urban Cape Colored patients with kwashiorkor was 48.9 per cent as compared with that of 23.5 per cent for the urban Cape Colored population in general.[34] Unlike the Africans and Asians the Cape Colored people do not recognize marriage ceremonies other than those of the Europeans, so the figure seems to reflect a marked degree of family instability in the patient's background.

Free indulgence in alcohol is very common among the Cape Colored men in a wine producing area. Among fathers of the patients the figure of 71 per cent for those who indulged freely is probably no higher than that for the rest of their socioeconomic group but the effects on the family may well be more significant when wages are erratic.

The possibility of stress within the mother-child relationship precipitating the acute stage of kwashiorkor has been raised by the studies by Geber and Dean[35] and by Farmer[7] in Kampala where accelerated culture

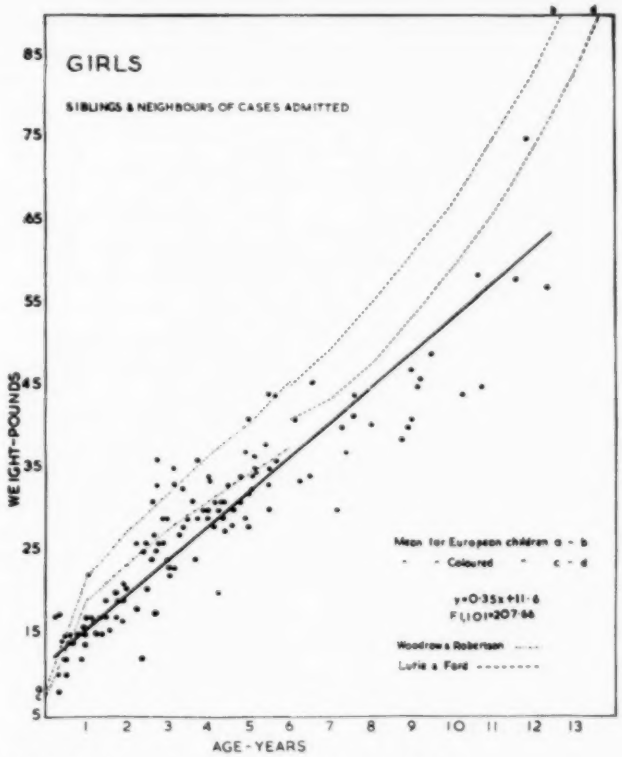

Fig. 4. Girls' annual increase in weight (pounds).

change seems to highlight this important factor. In the Cape Town series the incidence of prolonged emotional upset prior to acute symptoms was noted in 22 per cent of the cases. Geographic separation of the child from its mother is not a traditional practice among the Colored or the urban Bantu people at the age when kwashiorkor occurs at the Cape and, as has been shown, separation from the maternal breast has commonly occurred at a very tender age. Nevertheless, it did seem, in some instances, that the departure of the mother to work or to the hospital, or the birth of a sibling produced a "mourning reaction" in certain children, and that even a temporary rejection or deprivation of food might have caused a crisis in a child who was on a nutritional border line, which only the mother's constant attention and coaxing had prevented him from crossing.

THE SUBSEQUENT GROWTH AND RELAPSE RATE OF THE CHILDREN

Material and method. The homes of 132 patients who were in the hospital with kwashiorkor have been revisited on at least one occasion since discharge, most of them more often, and at approximately 3 month intervals. The patient's general condition and the family situation are noted and they are weighed and measured. Since many of the homes can be reached only on foot the scale used has had to be an easily portable one that gives a reasonable degree of accuracy and can be checked at intervals.

Results. Table IX records the general progress of the patients. Of the 11 deaths, 3 occurred after readmission to the hospital in a relapsed condition and 1 child died of kwashiorkor before admission. Three died after an attack of measles; one was reported

Table VI. Poverty underlying kwashiorkor in Cape Town

Below the Poverty Datum Line	*%*
Economic standard of the population of the area	52
Economic standard of homes of patients	82

Table VII. Income levels of families when kwashiorkor occurred and before kwashiorkor occurred

	Income when kwashiorkor occurred in families		*Income before kwashiorkor occurred in families*	
	No.	*%*	*No.*	*%*
No. of cases	138		81	
Below Poverty Datum Line	113	82	36	44
Slightly above Poverty Datum Line	19	14	27	33
Above the Effective Minimum Standard	6	4	18	23

to have been doing well until pneumonia developed; the cause of death in 2 was uncertain but was almost certainly nutritional in view of particularly poor home conditions and maternal care. The remaining 1, after a period of alleged family disruption and nonsupport, developed gastroenteritis; autopsy showed fatty changes in the liver.

Of the 10 who relapsed and recovered one had developed tuberculosis. Seven of the children were illegitimate including one who had an epileptic and mentally defective mother and one whose mother had absconded at an early stage in his life. One belonged to a family inadequately supported by a father, European in appearance, who had deserted them; one had excellent maternal care but succumbed to an acute infection after a period of poverty, the father being chronically disabled. A similar dreary story of intercurrent infection, poverty, unemployment, illegitimacy, nonsupport by fathers, and marital disruption was found among the children who were failing to gain weight.

It will be noted that in one third of the cases progress was unsatisfactory or the child had died. Since follow-up visits were starte while new cases were still being added to th series, the length of the observation perio varied from one child to the next. In Tabl X progress is shown in relation to the lengt of the follow-up period. The first 9 month after discharge appear to be the most criti cal in regard to consolidation of cure. Th few children who return home to a goo diet generally make excellent progress. Unde prevailing conditions, however, the majorit benefit for a while from their stay in th hospital and the initial effort of the mother, but after that they must take their chance with the rest of the family. In many cases the balance struck by the patient in the first year is a very precarious one, and, even if he is gaining weight, his survival from one visit to the next is by no means certain.

Surprise is often expressed[3, 6] at the number of patients who return to their former home environment and yet do not relapse. The explanation may lie in the point made in 3 recent articles[4, 7, 22] that kwashiorkor seems to mark the culmination of a series of stresses occurring at a particularly critical stage for that individual. It is understandable that this combination of

Table VIII. Employment history of fathers of patients and controls

	Kwashiorkor group		*Control group*	
	No.	*%*	*No.*	*%*
Total No.	99		128	
Employment nearly always regular	62	62	86	67
Moderately regular	13	13	21	16
Irregular or casual	24	24	21	16

Table IX. Progress of 132 patients visited after discharge from hospital

	No.	*%*	
Total No. of cases	132		
Gaining weight	88	66.6	
Became stationary in weight	12*	9.0	33.
Lost weight	11†	8.3	
Relapsed and recovered	10	7.5	
Died	11	8.3	

*In 4 cases failure to gain was temporary.
†In 3 cases loss of weight was temporary.

Table X. Progress of 132 patients in relation to period after discharge from hospital

Period of observation	Total number observed	Gained weight continuously	Ceased to gain weight*	Relapsed	Died
Under 1 to 3 months	30	21	5	2	2
3 to 6 months	24	10	6	4	4
6 to 9 months	30	17	8	2	3
9 to 12 months	17	15	1	0	1
12 to 15 months	23	19	2	1	1
15 to 18 months	8	6	1	1	0
Total	132	88	23	10	11

*In 7 cases loss of weight or failure to gain was temporary.

circumstances may not recur and that, if it does, the child may for a variety of reasons be better fitted to deal with it. When the home is known, it is sometimes possible to discern the saving factor in the situation, e.g., the child's having learned to walk or a mother's capacity for adapting her ways.

DISCUSSION

One of the features that differentiates kwashiorkor as it occurs in Cape Town from the syndrome as it occurs in most communities in Africa seems to be the earlier introduction of artificial feeding with its hazards of infection and overdilution. This is the case with both Cape Colored and African mothers who, in this respect, resemble the Indian and Negro mothers in Trinidad where Jelliffe and Symonds[36] report that in 21 per cent of a small series of cases breast feeding had never been established. The current study suggests, however, that the Cape population is not yet so far along the road of sophistication as that of Trinidad and that failure of lactation is at least as often due to the mother's poor nutrition, fatigue, and realistic anxieties as to her negative attitudes.[37] Her degree of success in lactation tends to fluctuate with change of circumstances from the birth of one child to the next, but there is still an acceptance of the desirability of natural feeding. If this can be encouraged, it may prove the strongest local asset in efforts to combat malnutrition. Despite authoritative statements on this question[38-40] very little is being done at present in the Cape Town area to feed pregnant and lactating mothers in order to produce healthier infants and to increase the latter's most valuable source of protein. As pointed out in the Wuppertal Report,[41] it is difficult to differentiate between the effect on lactation of poor nutrition and anxiety as the two so often go together but, in the Cape area at any rate, a good case could be made for the preventive value on both counts of supplementary feeding of mothers. It is emphasized that no claim is being made here for the superiority of breast milk as such. In the present context it is a practical question of a safe and adequate supply of milk for every young child.

A second finding of significance is the success of the child welfare clinics in preventing malnutrition among those who do avail themselves of the wide range of available services. The disturbing aspect is that so large a part of the population does not attend the clinics. There is an understandable tendency to consider that the mothers are too idle to do so but this makes no allowance for such factors as the distance of clinics, the time required to be absent from the home and other children, the failure to understand why a "well" child should go to a clinic, the inability to pay for the milk, the fear of reproof if money is not forthcoming, and the apathy engendered by prolonged poor nutrition, fatigue, slum living, ignorance, and limited intellectual ability. Since the local authorities, from their limited resources, must supply the milk, the clinics need to consider first the most needy age groups, and infants thus have priority over the children most liable to develop kwashiorkor. Hospital statistics also show the high incidence of other diseases to which poor nutrition is a contributory factor.

It appears that the basic remedy for malnutrition in Cape Town must be an economic one and that this will have to be supplied by both short- and long-term planning, the former in relation to subsidized food supplies, probably in the form of supplemented cereals; the latter in relation to wage structure and labor conditions. Second, the widespread ignorance requires a campaign of health education under the guidance of trained experts in this field working through child welfare personnel, hospitals, schools, dietetic departments, and voluntary organizations and relying as much on small unit discussion groups as on mass propaganda. Third, the whole gamut of social disorganization needs to be met, again by short- and long-term planning, the former directed toward increased housing and welfare facilities, community activities, and other measures to encourage the establishment of responsible family life; the latter toward promoting a climate in which ability can reach its optimum development, and frustration can be minimized.

SUMMARY

1. The background of 150 hospitalized cases of severe kwashiorkor has been studied with the use of the patients' siblings as controls. At the same time the growth rates have been recorded of various children who lived in the same social setting as the patients but who had not developed kwashiorkor.

2. These studies indicate that the disease tends to occur among child populations that show widespread evidence of growth retardation. Other pertinent findings are early failure of lactation and dietary deficiency associated with poverty, ignorance, prevalence of infection, and a general state of poor housing and social disorganization among unskilled laborers in an area of rapid industrial development.

3. Preliminary results are given for the progress of 132 cases visited at least once within 18 months of their discharge from the wards. Of these 67 per cent had gained weight continuously; 25 per cent had become stationary in weight, had lost weight, or had relapsed; and 8 per cent had died. Most of these failures occurred during the first 9 months after discharge. The follow-up study is designed to extend for 5 years.

I am deeply indebted to Professor J. F. Brock and Dr. J. D. L. Hansen for reading this paper and offering invaluable suggestions; to the ward sisters, social workers, and administrative staff of the two hospitals for their unfailing cooperation, and to Professor F. J. Ford for facilities in the Department of Child Health. Miss Gravett and Mr. P. Sand of the Department of Mathematics calculated the regression slopes and Dr. B. Bronte-Stewart was consulted on some problems of interpretation. Particular thanks are due to Dr. P. M. Smythe who was the first to encourage the undertaking and has maintained a helpful interest in it throughout.

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MEDICAL PROGRESS

Severe acquired mitral stenosis in childhood and adolescence

With special reference to radiographic and phonocardiographic features

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DURHAM, N. C.

ALTHOUGH acquired critical or tight mitral stenosis is predominantly a disease of adults, recent reports have pointed out that occasionally this disorder may develop in childhood or early adolescence.[1-4] Successful valvuloplasty has been performed in a child of 7 years[2] and postmortem findings are described by Johnson and Lewes[5] in a patient of 3 years with severe mitral stenosis, alleged to be of rheumatic origin.

In the years since 1948 when successful commissurotomy was first performed by Bailey,[6] great advances have been made in the understanding of the physiologic derangements in mitral stenosis. Cardiac catheterization studies have furnished invaluable information about the altered hemodynamics, permitting a correlation of direct physiologic measurements with the clinical state, physical examination, x-ray, electrocardiogram, and phonocardiogram. Consequently, it is now possible in a majority of instances to evaluate the patient with mitral stenosis on the basis of these simpler and less expensive techniques.

It is the purpose of this paper to discuss the hemodynamic alterations and the resultant clinical manifestations in mitral stenosis. We shall emphasize the valuable information to be gained from the simple special studies, particularly the x-ray and phonocardiogram.

Our experience with 5 young patients over the past several years has stimulated us to prepare this review. These cases, which have exhibited virtually all the importan

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features of mitral stenosis, are presented in Table I. All the illustrative x-rays, electrocardiograms, and phonocardiograms are drawn from these cases.

NATURAL HISTORY

In the initial attack of rheumatic carditis extensive pathologic changes may occur in both valves and myocardium. Valvulitis is characterized by formation of verrucae, damage to the endocardial layer, lymphocytic infiltration, and valvular edema.[7] Cardiac muscular damage, when severe, consists of diffuse or focal myocardial necrosis and inflammatory infiltration. In the milder cases, however, the myofibers may recover or regenerate.[8] It is the myocarditis per se which is of overwhelming clinical importance in the acute episode, although valvular involvement in the form of mitral (and aortic) insufficiency is of unquestioned importance in producing characteristic regurgitant murmurs and increasing the work load of an already impaired myocardium.

A low-pitched apical diastolic murmur is commonly noted during the acute rheumatic episode, especially in patients with severe carditis. This murmur, originally described by Coombs,[9] represents a functional or relative mitral stenosis. Cardiac dilatation is probably only a partial basis for this murmur inasmuch as similar murmurs are infrequent in the various forms of diffuse nonrheumatic myocarditis without valvular involvement. This suggests that mitral regurgitation and the resultant augmented left atrial volume at the end of systole set the stage for increased flow across the valve in early diastole. It is probably the combined effects of large blood flow across an abnormal valve into a dilated ventricle that produce this rumbling murmur of so-called relative stenosis.

Although acute valvulitis is the process initiating ultimate organic stenosis, two theories have been advanced as to the exact mechanisms involved. A commonly accepted theory is that the acute inflammatory process initiates very slow cicatricial contraction of the valve, a wholly intravalvular process. An older theory, originally proposed by Rokitansky over 100 years ago and recently supported by Magarey,[10] proposes organization of long-term fibrin deposits on both valves and chordae as of prime importance in the pathogenesis of the stenosis.* We still remain ignorant, however, of the factors controlling rate of development of stenosis and why, in some patients, a pure stenosis develops while in others insufficiency is the dominant lesion.

Although the time from onset of the acute attack of carditis to the stage of significant stenosis varies considerably, it is almost never less than 2 years and most commonly is from 6 to 20 years.[11, 12] Worthy of emphasis is the fact that the initial rheumatic episode is often subclinical in patients destined to develop dominant stenosis, a feature which was stressed some years ago in the classic paper by Walsh, Bland, and Jones.[11] Of our patients, 3 of 5 gave no history to suggest an acute attack of rheumatic fever.

Subclinical deterioration in cardiac function is noted as the mitral valve area reaches 2.5 to 2 sq. cm. or about one half the usual valve area. According to Likoff, the earliest physiologic change is the establishment of an abnormal diastolic pressure gradient across the valve without an absolute elevation in left atrial pressure.[13] Other physiologic functions remain essentially normal, however, including the ability to increase cardiac output with exercise.

As the valve area approaches 1 sq. cm., flow across the valve decreases appreciably in spite of rises in left atrial pressure.[13] The latter measurement is often quite labile, increasing at first only during exertion. The important relationship between mitral valve area and flow rates at different levels of left atrial pressure is well shown in Fig. 1 from Gorlin.[53]

With elevation in left atrial pressure, passive pulmonary congestion ensues, and the stage is set for symptoms such as dysp-

*It is unknown whether fibrin deposition occurs episodically or continually.

Table I

	Patient 1, C. J.	*Patient 2, W. J.*
Sex and race	Male Negro	Female white
History of acute rheumatic fever	Age 7. Polyarthritis and carditis. Mitral and aortic regurgitation	None
Age at onset of symptoms of mitral stenosis	Insidious onset, approximately at age 12	Insidious onset, approximately at age 12
Time between onset of symptoms of mitral stenosis and establishment of diagnosis	12-24 months	12-18 months
Age at operation	15 9/12	13 0/12
Symptoms ascribed to mitral stenosis	Progressive dyspnea on exertion. Paroxysmal nocturnal dyspnea	Angina and dyspnea on exertion. Paroxysmal nocturnal dyspnea
Physical examination	Moderate cardiomegaly. Loud M-1. Soft apical systolic murmur. Loud unsplit second sound. Opening snap. Apical presystolic rumble	Height and weight below third percentile. Malar flush. Mild cyanosis. Slight cardiomegaly. Loud M-1. No systolic murmur. Loud unsplit P-2. Opening snap. Holodiastolic apical rumble
Electrocardiogram	Sinus rhythm. Right and left atrial enlargement. RAD and severe RVH	Sinus rhythm. Left and right atrial enlargement. RAD and moderate RVH (Fig. 10)
Radiographic studies	*Age 12:* Moderate cardiomegaly. Increased venous markings *Age 15:* Moderate cardiomegaly. Large main pulmonary artery segment. Moderate left atrial enlargement. Diffuse venous and arterial narrowing	Moderate cardiomegaly. Double shadow of left atrial enlargement on posteroanterior film. Large main pulmonary artery segment with striking basilar arterial constriction. Narrowed basilar veins and engorged upper lobe veins (Fig. 8)
Preoperative phonocardiographic index (see text)	Q-1 = .09 sec. 2-OS = .05 sec. Index = +4	Q-1 = .09 sec. 2-OS = .08 sec. Index = +1
Special studies	No catheterization. At beginning of operation, the patient's condition deteriorated so that pressures were not obtained. Immediately after valvulotomy pulmonary artery pressure was 80/50	No catheterization. At operation pulmonary artery pressure was 75/32 and left atrial pressure was 30/20. After valvulotomy, these pressures were 60/25 and 14/6 respectively
Surgical findings	Mitral valve markedly calcified. Estimated area 0.5 cm.^{2}	Both commissures fused and uncalcified. Estimated valve area 0.5 cm.^{2}
Left atrial biopsy	Numerous Aschoff bodies	Numerous Aschoff bodies
Postoperative status	Transient hemiparesis postoperatively. Marked symptomatic improvement. However, re-emergence of signs of aortic valve disease (aortic stenosis and regurgitation) was noted	Improved exercise tolerance. Striking growth spurt. No residual murmurs evident until 4 months after operation when a faint apical protodiastolic murmur appeared
Postoperative phonocardiographic index	Q-1 = .08 sec. Opening snap not identified	Q-1 = .06 sec. 2-OS = .09 sec. Index = −3

Abbreviations: M-1 = Mitral first sound. P-2 = Pulmonic second sound. RAD = Right axis deviation. RVH = Right ventricular hypertrophy. Q-1 = Time between onset of Q wave of ECG and mitral valve closure. 2-OS = Time between first aortic component of second sound and opening snap. P"C" = Pulmonary "capillary."

Patient 3, M. M.	*Patient 4, I. R.*	*Patient 5, L. G.*
Female white	Female white	Female white
Age 9. Polyarthritis and mild carditis with mitral regurgitation	None	None
Insidious onset, approximately at age 10	Insidious onset, approximately at age 10	Abrupt onset (hemoptysis) at age 14
6-12 months	24-30 months	5 months
15 10/12	15 9/12	Died before operation
Mild, nonprogressive dyspnea on exertion	Progressive dyspnea on exertion. Hemoptysis	Hemoptysis. Dyspnea. Fatal pulmonary edema (first episode)
Minimal cardiomegaly. Loud M-1. Soft apical holosystolic murmur. P-2 slightly accentuated and normally split. Opening snap. Holodiastolic apical rumble with presystolic accentuation	Moderate cardiomegaly. Loud M-1. No systolic murmurs. Loud P-2. Opening snap with apical holodiastolic rumble and presystolic crescendo	Malar Flush. Loud M-1. No systolic murmurs. Opening snap. Holodiastolic apical rumble with presystolic accentuation
Sinus rhythm. Normal P waves. Slight RAD and borderline RVH	Sinus rhythm. Left atrial enlargement. RAD and slight RVH	Sinus rhythm. Tracing probably within normal limits (Fig. 9)
Minimal cardiomegaly. Moderate left atrial enlargement with double shadow on posteroanterior film. *Age 12:* Diffuse venous congestion. *Age 13½:* Basilar venous and arterial narrowing. Engorged upper lobe veins. Kerley's lines (Fig. 6)	Minimal cardiomegaly. Moderate left atrial enlargement with double shadow on posteroanterior film. Large left atrial appendage. Basal arterial and venous narrowing. Engorged upper lobe veins. Kerley's lines (Figs. 3 and 7)	Slight cardiomegaly. Moderate left atrial enlargement with double shadow on posteroanterior film. Engorged upper lobe veins. No arterial changes evident (Fig. 5)
Q-1 = .10 sec. 2-OS = .06 sec. Index = +4	None preoperatively	2-OS = .05 sec.
Cardiac catheterization. *Age 12:* Pulmonary artery pressure 26/13 at rest and 32/21 with exercise. P"C" pressure 15 at rest and 23 with exercise	Cardiac catheterization. *Age 15 9/12:* Pulmonary artery pressure 25/13 at rest and 36/18 with exercise. No P"C" pressures. Cardiac output fixed at 3.2 liters per minute	No special studies or surgery. No postmortem examination
Small regurgitant jet. Uncalcified valve with estimated area slightly less than 1.0 cm.²	Small regurgitant jet. Uncalcified mobile valve with estimated area less than 1.0 cm.²	
Aschoff bodies present	No Aschoff bodies	
Improved exercise tolerance. Moderate growth spurt. Moderate residual mitral regurgitation	Marked improvement in exercise tolerance. Growth spurt. A faint holosystolic apical murmur appeared postoperatively. A short apical protodiastolic rumble persisted	
Q-1 = .08 sec. 2-OS = .07 sec. Index = +1	Q-1 = .08 sec. 2-OS = .08 sec. Index = 0	

nea on exertion, orthopnea, and hemoptysis to appear. It is now that the individual also may become susceptible to bouts of pulmonary edema, during which left atrial pressure rises and pulmonary capillary pressure temporarily exceeds plasma oncotic pressure (about 25 mm. of mercury). This results in transudation of fluid into the alveoli and the appearance of the well-known symptoms and signs of pulmonary edema. Cardiac output is well maintained in these episodes[15] although inordinate increases in pulmonary artery pressure and right ventricular work are the rule.[16] It should be emphasized that resting pulmonary artery pressure may be normal or but slightly elevated in patients subject to bouts of pulmonary edema.

In any consideration of mitral stenosis, especially with reference to the development of pulmonary edema, the important deleterious effect of tachycardia must be recognized. Indeed, the decrease in diastolic filling time which accompanies increases in heart rate further impairs the emptying ability of the left atrium. As this occurs, pulmonary venous and capillary pressures rise and dyspnea, orthopnea, or frank pulmonary edema appears. The anxiety attending development of shortness of breath may result in further increase in tachycardia and progression of the acute episode. Although spontaneous subsidence of milder symptoms is the rule, severe bouts of pulmonary edema demand prompt and vigorous therapy, including digitalis, oxygen, rotating tourniquets, and morphine. The latter drug is extremely useful, possibly to a significant extent, by decreasing the systemic venous return through allaying anxiety and diminishing purposeless skeletal muscular activity. Nonetheless, its specific action in pulmonary edema suggests additional unique effects which may include selective direct or reflex effects on the pulmonary vascular bed, tending to decrease transudation into the air spaces.

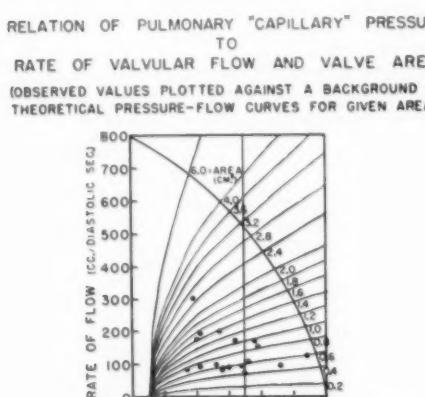


Fig. 1. The importance of valve area in determining the relationship between pulmonary "capillary" (left atrial) pressure and mitral valve flow. Note that with the smaller valve areas, large increases in pulmonary "capillary" pressures are associated with little augmentation of mitral flow. from Gorlin and Gorlin: Am. Heart J. 41: 1, 1951.)

Elevation of pulmonary arterial pressure in mitral stenosis depends on mechanisms beyond simple passive congestion. Nevertheless, the latter process may be of great importance as a prime factor stimulating reactive muscular constriction of the smaller pulmonary arteries and the veins as well. The presence of a pulmonary vasoconstrictive process[17-23] probably explains the lack of correlation in many patients between the calculated pulmonary vascular resistance and histologic evidence for organic vascular changes.[22] Although some degree of reactive pulmonary vasoconstriction is probably present in a majority of patients with tight mitral stenosis, there is considerable individual variation in the severity of this process (Fig. 2).* In an advanced stage, all anatomic regions of the lungs may be involved. However, involvement of different portions of the lungs evidently follows a fairly predictable sequential pattern with initial changes appearing in the lower lobes. Regional vascular alterations affecting both the arterial and venous sides of the pul-

*In a minority of patients, arterial vasoconstriction is so severe that the clinical profile is more nearly that seen in primary pulmonary hypertension rather than typical mitral stenosis. As in primary pulmonary hypertension, this reaction in mitral stenosis is prone to develop in young females.[15]

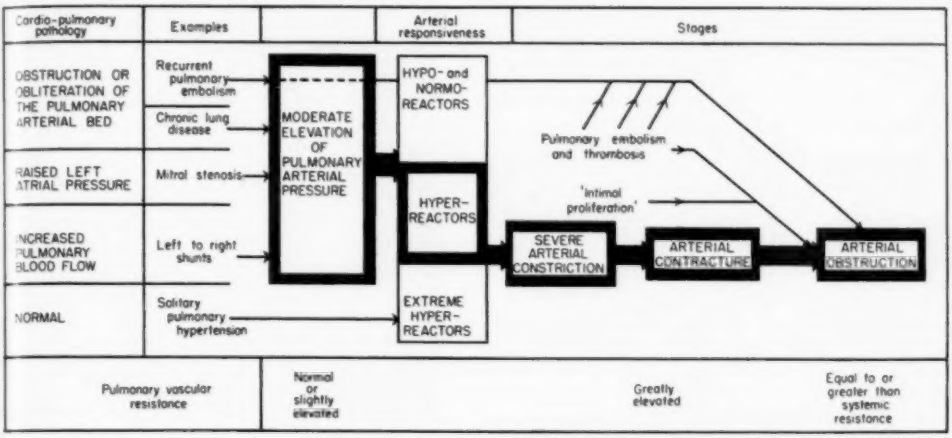


Fig. 2. A suggested pathogenesis of pulmonary hypertension. (From Short: In Adams, W. R., and Veith, L., editors: Pulmonary Circulation, New York, 1959, Grune & Stratton, Inc., by permission.)

monary vascular bed provide characteristic radiographic findings. These will be discussed in a later section.

Although functional vasoconstriction of the pulmonary vessels is probably an important mechanism in mitral stenosis, it also must be realized that organic vascular changes which are apparently largely irreversible do develop. Fortunately, a significant degree of obliterative vascular disease is in most instances a late development. Much recent interest has centered on pharmacologic means to distinguish and quantitate the importance of the vasoconstrictive versus the structural factor in pulmonary hypertension. Techniques such as having the patient breathe 100 per cent oxygen or the administration of compounds such as acetylcholine,[13] hexamethonium,[23] or Priscoline[24] have proved useful in this regard.

Progressive pulmonary vascular changes in severe mitral stenosis result in pulmonary hypertension, right ventricular hypertrophy, and eventual right-sided decompensation. In these later stages, the patient becomes less prone to bouts of pulmonary edema, probably as a result of the combined effects of the fixed low output of the right ventricle along with thickening of the pulmonary capillary walls, the latter factor tending to increase the pressure required to produce transudation of fluid into the alveoli. Thus, the decreased incidence of pulmonary edema in advanced mitral stenosis is a further reflection of progressive hemodynamic deterioration. We concur with Donald who states that this is "not an adaption in the biological sense but merely one fortunate turn of events amidst many unfortunate ones."[13]

In most patients destined to develop critical mitral stenosis the initial rheumatic episode is mild and not apt to be associated with extensive myocarditis. Nevertheless, the status of the myocardium must be considered in patients with mitral stenosis since underlying rheumatic damage to cardiac muscle may be a factor in hastening decompensation[25] and in rendering the results of medical and surgical therapy less than optimal.

RADIOGRAPHIC FEATURES OF MITRAL STENOSIS

Radiographic examination of the chest furnishes invaluable information in patients with mitral stenosis. Pertinent changes involve both the heart and the pulmonary vasculature and indeed, at least with respect to evaluation of pulmonary hypertension, vascular alterations may be more important than those involving the heart. In this discussion the value of plain films will

be emphasized. However, cardiac fluoroscopy can occasionally furnish useful supplementary information, especially with reference to specific chamber enlargement.

Less increase in over-all heart size is present in patients with pure mitral stenosis than in those with significant associated mitral regurgitation. In fact, the over-all size of the cardiac silhouette may occasionally be within normal limits in severe stenosis. Usually, however, some cardiomegaly is present, especially with higher grades of associated pulmonary hypertension.[26, 27]

More important than total heart size in evaluation of the patient with mitral disease are the size and contour of the left atrium. Mild to moderate degrees of left atrial enlargement accompany severe mitral stenosis, and on plain posteroanterior films this can be recognized as a double shadow to the right of the midline in about 75 per cent of the patients.[28] This is usually associated with elevation of the left mainstem bronchus. Furthermore, examination

Fig. 3. Lateral radiogram in patient with severe mitral stenosis (Patient 4). The lateral film demonstrates the characteristic focal indentation of the barium-filled esophagus by the enlarged left atrium.

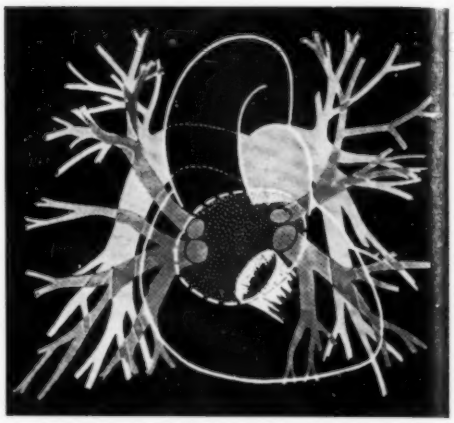


Fig. 4. Tomographic reconstruction diagram of the normal relationships between the pulmonary veins and arteries. (The darker shaded structures are the veins.) (From Simon, M.: J. Fac. Radiol. 9: 15, 1958, by permission.)

of the lateral or right anterior oblique films, especially with barium in the esophagus, demonstrates that more than 90 per cent of patients have obvious left atrial enlargement.[28] In pure stenosis the barium-filled esophagus usually is indented superiorly in a circumscribed fashion (Fig. 3), while in dominant mitral regurgitation there is generalized backward displacement of the esophagus in a wide sweeping arc along the entire posterior cardiac border.[29] From the foregoing it should be evident that higher grades of left atrial enlargement are uncommon in dominant mitral stenosis, and, when present, should alert the physician to the possibility that regurgitation is the major lesion.

A word of caution is in order with regard to systolic expansile pulsation of the left atrium. As Steiner and Goodwin[30] point out, this finding should be regarded only as a sign of mitral valve disease and cannot be used as a reliable guide to the presence of significant associated mitral regurgitation.

Ventricular predominance deserves careful evaluation. In pure mitral stenosis there should be little or no evidence for left ventricular enlargement. Consequently, displacement of the cardiac apex downward

and outward on the posteroanterior and left anterior oblique films is not to be expected and, if present, should again alert one to the possibility of significant associated mitral (or aortic) regurgitation. On the other hand, radiologically evident right ventricular hypertrophy is often present in moderate and severe grades of stenosis, especially when there is associated pulmonary arterial hypertension. This is characterized by outward and upward displacement of the cardiac apex and obliteration of the retrosternal space in the lateral and right anterior oblique views.

The aorta is usually small in mitral stenosis. In fact, Dealy[29] has found this rather consistently in more severe grades of mitral stenosis. Thus, a normal-sized or large aorta may indicate mild stenosis and/or an associated aortic lesion.

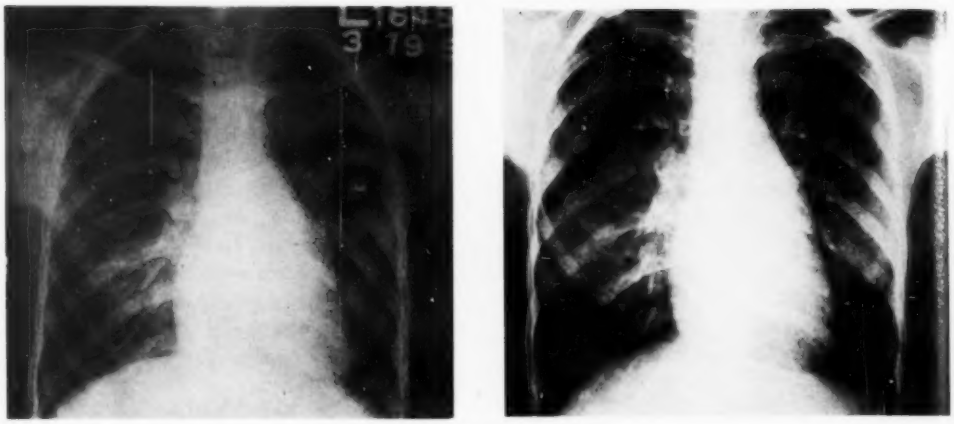
In mitral stenosis, important radiologic changes occur in the pulmonary veins and arteries. Fig. 4 demonstrates the anatomic relationship between these structures. It should be noted that the central portions of the veins lie considerably below the right and left main pulmonary arteries (about 2 inches in the adult) and that the course of the lower and middle lobe veins is quite different from that of the corresponding arteries. On the other hand, in the upper lobe, the veins run parallel and slightly lateral to the arteries.[31]

The first link in the chain of events involving the pulmonary vascular system in mitral stenosis is passive congestion of the pulmonary venous system (Fig. 5). In the upright position, however, hydrostatic factors result in a considerable difference in the degree of pulmonary venous hypertension in the upper and lower lobes. Lower lobe venous pressures reach relatively high levels early in the disease and, according to Simon,[31] serve as a stimulus to both pulmonary venous and arterial vasoconstriction in the basal regions. This apparently results in a shift in pulmonary blood flow with a compensatory increase in the circulatory volume in the upper lobes. In this connection Simon feels that the upper lobe veins become engorged not so much as a result of passive congestion but as a manifestation of the increased flow to the upper lobes. Radiologically evident engorgement of the upper pulmonary veins becomes evident somewhat earlier than do the associated peripheral arterial changes (see below). Furthermore, it appears that the most marked degree of pulmonary venous engorgement is noted with left atrial pressures near 25 mm. Hg. Above this level the veins become less prominent, possibly reflecting the upward progression of the venous vasoconstrictive process.[31]

Damman[31a] has compared the histologic pattern in the upper and lower lobes in patients with mitral stenosis. He observed that in the not too long-standing case, for example, the upper lobe capillaries, veins, and arteries might be dilated, congested, and minimally thickened while, in the same patient the lower lobe arteries, and often the capillaries and veins as well, might show marked thickening.

By means of external counting over the

Fig. 5. Posteroanterior chest film in patient with severe mitral stenosis but no evidence of significant pulmonary hypertension (Patient 5). This film, taken 9 days prior to a fatal episode of pulmonary edema, shows slight cardiomegaly and prominent pulmonary venous congestion, most marked superiorly. Arterial changes are not evident.



A *B*

Fig. 6. Serial pulmonary vascular changes in mitral stenosis (Patient 3). These preoperative films, taken 19 months apart, demonstrate progressive changes. The earlier film *(A)* shows prominence of the left atrial appendage and generalized venous engorgement. Arterial changes are not evident. The later film *(B)* shows a decrease in venous markings along with basilar arterial narrowing. Kerley's lines become evident in later films. However they are not shown well here.

chest, Dollery and West[31b] have monitored the pulmonary uptake of radioactive oxygen, carbon monoxide, and carbon dioxide in normal subjects and patients with mitral stenosis. They have found that individuals with mitral stenosis, particularly those with high pulmonary artery pressures, have higher blood flows through the upper portions of the lung than through the lower sections. This flow pattern is the reverse of that found in normal persons and correlates well with observed radiographic and histologic changes in mitral stenosis.

The main pulmonary artery and its larger branches are usually obviously enlarged in mitral stenosis.[26-30, 32*] Moore and associates[32] have recently shown that, while the relationship between pulmonary artery size and degree of pulmonary hypertension is direct, it is not linear. Interestingly, this relationship, when plotted graphically, resembles a pressure volume curve, a not wholly unexpected finding. It is important to point out that the absence of obvious increase in size of the larger pulmonary arteries may be a very helpful finding in excluding moderate and severe grades of pulmonary hypertension.[26]

The radiologic evaluation of the pulmonary arterial system in a patient with mitral stenosis should not stop with the larger vessels, for of equal if not greater significance are the changes involving the more peripheral arteries, those normally measuring 2 to 5 mm. in diameter (Figs. 6, 7, 8). These changes have been noted by several authors[27, 30-34] and consist of narrowing and increased tortuosity of the peripheral vessels, the earliest and most evident changes involving those arteries supplying the basal regions. The contrast between the enlarged central and the narrowed peripheral vessels is often striking and usually best appreciated in the portions of the arterial tree supplying the right lower and middle lobes. The diminution in caliber of the smaller vessels is thought, at least in the earlier stages, to represent largely functional vasoconstriction of the arteries. In long-standing disease however, superimposed organic vascular changes are to be expected.

Another of the radiologic features of mitral stenosis are lines "B" of Kerley, nar-

*In patients of or approaching adult body size, we regard 14 mm. as the upper limit of transverse diameter of the right main pulmonary artery.

row horizontal lines generally 2 to 3 cm. in length, located near the costophrenic angles (Figs. 6, 7). The origin of these shadows has been a matter of some debate. However, at present most observers feel that they represent engorged pulmonary lymphatic channels.[35, 36] Kerley's lines are specific for conditions associated with pulmonary venous hypertension and are not found in patients with the commoner congenital lesions such as ventricular septal defect, patent ductus, etc., which may be associated with severe pulmonary hypertension.[36] They may be absent at one examination and present at the next, perhaps relating to differences in patient activity (and hence hemodynamic status).[37] Nevertheless, there is a general correlation between the presence of Kerley's lines and severity of disease. If they are obvious, it is probable that pulmonary venous pressure is high. The reader should be cautioned, however, that these lines may be seen when there is significant associated mitral regurgitation. Furthermore, as Carmichael and coworkers[38] point out, little significance should be ascribed to them in the presence of pleural effusion, gross cardiomegaly, congestive failure, basal emphysema, recent pulmonary infarction, and acute pulmonary edema.

From the foregoing it is evident that there are many facets involved in the radiologic evaluation of the patient with mitral stenosis, and that a number of the changes are quite subtle. Nevertheless, given a reasonable background of experience, the physician should find the x-ray of considerable value in his appraisal of the patient with mitral disease in terms of both the cardiac and pulmonary vascular changes.

ELECTROCARDIOGRAM

The electrocardiographic changes in critical mitral stenosis depend to a large extent on the duration of the disease and the severity of associated pulmonary hypertension (Figs. 9, 10). M-shaped or so-called mitral P waves are common although frequently the P waves are broad or flat topped but not clearly notched.[39] Moreover, in some patients they may be normal. Definite electrocardiographic evidence of right ventricular hypertrophy, especially when there is associated right axis deviation, strongly suggests significant pulmonary hypertension.[40, 41]

AUSCULTATORY AND PHONOCARDIOGRAPHIC FEATURES

The alteration of the cardiac sounds and the character of murmurs in mitral stenosis are themselves a complex subject which can only be summarized here. For a more complete review, the reader is referred to the recent texts by Friedberg,[42] McKusick,[43] and Levine and Harvey[44] and to the excellent papers by Hultgren and Leo[45, 46] and Ongley and his associates,[47] to mention but a few.

The mitral component of the first sound is abnormally loud and ringing in quality in mitral stenosis. Although other factors may be involved, the intense first sound is ascribed largely to alteration in the sound-generating characteristics of the valve secondary to fibrotic changes. Not only is mitral closure abnormally loud, but it is frequently delayed when timed from the onset of the QRS complex of the electrocardiogram. This had been thought to be due to the additional time required for the left ventricle to overcome an elevated left atrial pressure. However, Rich,[48] in a recent study, was unable to find any relationship between the delay in the first sound and the height of left atrial pressure.* Further, he presented evidence that a more likely explanation related to the poor ventricular filling in mitral stenosis with the correspondingly slower rate of rise of intraventricular pressure.

Occasionally systole may be completely silent in "pure" mitral stenosis. However, there may be an apical holosystolic murmur reflecting trivial mitral regurgitation and/or

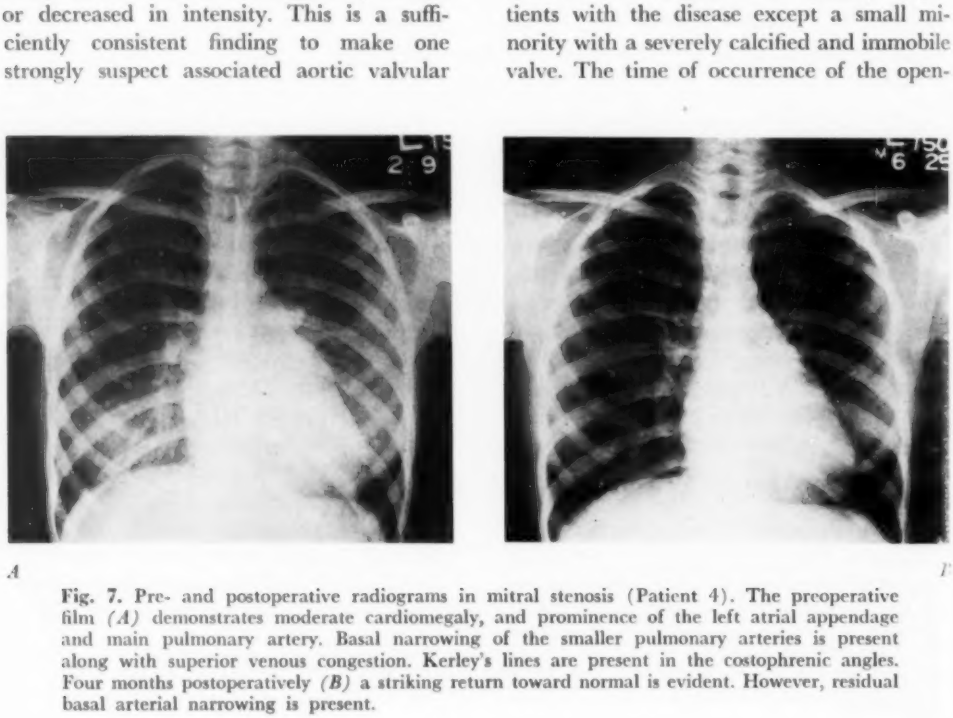
*For these purposes Rich[48] measured left atrial pressure at the height of the C wave. It is at this point in the cardiac cycle that the mitral valve closes.

an early-mid systolic ejection murmur arising in the dilated pulmonary artery. The latter is loudest over the second left intercostal space parasternally but is well transmitted over the entire precordium. Incidentally, an early systolic click or ejection sound may also be present over the pulmonary area, especially where there is significant pulmonary hypertension.

In any condition associated with right ventricular hypertension and/or dilatation, the murmur of tricuspid regurgitation may appear. This is typically a blowing holosystolic murmur, usually loudest in a location medial to the apex. This murmur is often accentuated during inspiration (Carvallo's sign), a feature which at times may be helpful in separating it from the murmur of mitral regurgitation.

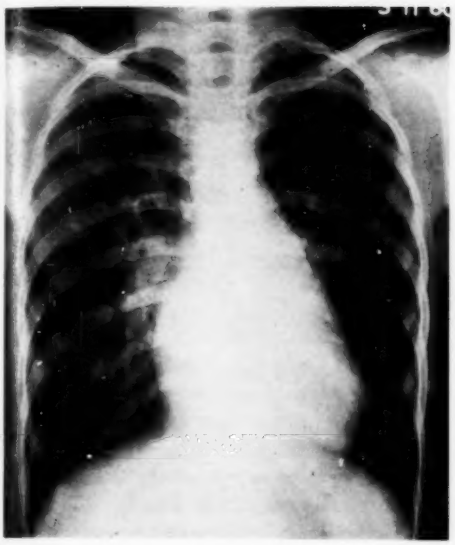
The pulmonic component of the second sound is usually of increased intensity in mitral stenosis, another finding correlating in a very general way with the degree of pulmonary hypertension. The aortic second sound on the other hand is generally normal or decreased in intensity. This is a sufficiently consistent finding to make one strongly suspect associated aortic valvular disease in a patient with mitral stenosis and a loud A_2. In patients with normal or minimally elevated pulmonary artery pressures, physiologic variable splitting of the second sound is present but as pulmonary hypertension develops the second sound becomes single. However, in any patient the impression of prominent splitting may be given because of the presence of an opening snap. The separation of the components of the second sound from an opening snap may be impossible unless, as Ongley and collaborators[47] point out, a simultaneous apex cardiogram is recorded.

The opening snap is a most important auscultatory finding in mitral stenosis. It is a brief, high-frequency, clicking, early diastolic sound which is often well heard at the base or midway between the apex and the pulmonic area rather than the apex. It is an audible exaggeration of the normally inaudible mitral valve opening sound and results again from the changed sound-generating capacity of the fibrous and thickened valve. It is present in virtually all patients with the disease except a small minority with a severely calcified and immobile valve. The time of occurrence of the open-



A *P*

Fig. 7. Pre- and postoperative radiograms in mitral stenosis (Patient 4). The preoperative film *(A)* demonstrates moderate cardiomegaly, and prominence of the left atrial appendage and main pulmonary artery. Basal narrowing of the smaller pulmonary arteries is present along with superior venous congestion. Kerley's lines are present in the costophrenic angles. Four months postoperatively *(B)* a striking return toward normal is evident. However, residual basal arterial narrowing is present.



A

ing snap with the first or aortic component of the second sound used as a reference point, reflects the severity of the stenotic process. That is, with higher left atrial pressures, mitral valve opening occurs earlier or closer to the second sound.

The temporal relationship of the opening snap to the second sound may be incorporated with the delay in the first sound to formulate a phonocardiographic index of severity.[49, 50] This, the (Q-1) minus (2-OS) time, is derived by subtracting the time from the onset of the second sound to the opening snap (2-OS time) from the interval between onset of the Q wave of the electrocardiogram and the first major component of the first sound (Q-1 time). Positive figures usually reflect a process of at least moderate severity (valve area 1.2 sq. cm. or less). At slow rates this index may be misleading since, with a longer diastole, more efficient decompression of the left atrium may be achieved and the Q-1 time shortens and the 2-OS time is prolonged.[50]

There are in reality two apical diastolic murmurs to be considered in mitral stenosis, the protodiastolic and the presystolic. The former begins in early diastole and is initiated by the opening snap. It is generated during the phase of passive filling, that part of diastole normally accounting for some 70 to 90 per cent of ventricular filling. This murmur may be short in mild stenosis but tends to lengthen as the degree of obstruction becomes more severe.[46]

In hemodynamically significant mitral stenosis, the contribution of atrial contraction to ventricular filling assumes greater importance and, in the absence of atrial fibrillation, a crescendo presystolic murmur usually is evident. This, as McKusick,[43] Leatham,[51] and others have shown, should be considered an atrial ejection murmur which in the presence of first degree heart block can be demonstrated to be a crescendo-decrescendo murmur. However, with normal P-R intervals, the onset of the next first sound interrupts the murmur, obliterating its latter half or decrescendo phase.

Auscultation for the murmurs of mitral stenosis should be carried out initially with the patient supine and then, as Levine and Harvey[44] point out, during the act of turn-

B

Fig. 8. Plain posteroanterior chest radiogram *(A)* and venous angiogram *(B)* in patient with mitral stenosis and severe pulmonary hypertension (Patient 2).

Pulmonary artery pressure at operation was 75/32 mm. Hg. The angiogram strikingly demonstrates the basilar arterial oligemia which is seen in mitral stenosis with pulmonary hypertension. Similar changes are evident, although less dramatically shown on the plain film.

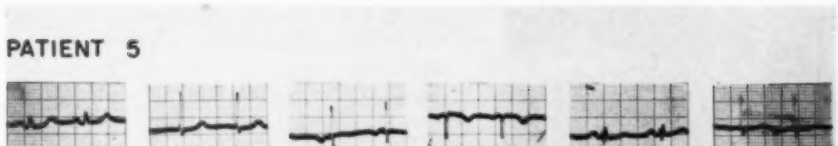


Fig. 9. Patient 5. This 14-year-old patient had severe mitral stenosis, but little evidence of pulmonary hypertension. The electrocardiogram is probably within normal limits.

ing to the left lateral decubitus position. Other maneuvers, such as more vigorous exercise and the use of amyl nitrite, may also be helpful. The examiner must remember that these murmurs may be very circumscribed in location so that careful stethoscopic exploration of the apical area is sometimes required. The low-pitched nature of the diastolic murmurs dictates that the bell of the stethoscope be employed. It should be applied very lightly to the chest wall.

CARDIAC CATHETERIZATION

A detailed discussion of the techniques of cardiac catheterization is beyond the scope of this review. Standard right heart catheterization furnishes a variety of physiologic information. Of particular interest in mitral stenosis are the right ventricular, pulmonary artery, and pulmonary "capillary" (wedge) pressures, the latter furnishing an approximation of the pulmonary venous pressure. Also, the cardiac output,[32] cardiac index,[32*] pulmonary vascular resistance,[32] and the mitral valve area[33] may be calculated.

The responses of certain hemodynamic variables to exercise are often studied. Patients with severe mitral stenosis, but a functionally adequate myocardium, may show little or no exertional increase in cardiac output, but exercise may result in inordinate rises in pulmonary artery and right ventricular systolic and diastolic pressures,[34] along with a marked increase in the pulmonary wedge pressure.

The various methods of left heart catheterization would appear to offer the most direct approach available to the study of mitral valve disease, since direct left atrial and left ventricular pressure tracings may be obtained and the pressure gradient across the mitral valve may be measured. Also, recognition of associated mitral regurgitation is possible. These techniques are relatively new and involve more risk than routine venous catheterization.

We believe that in the patient with straightforward mitral stenosis neither right nor left heart catheterization is essential. Moreover, any data obtained from laboratory studies of this type must be regarded as ancillary information to be integrated with the total clinical picture. There is a widespread tendency to overemphasize the results of cardiac catheterization. When this is done, especially to the extreme of discarding apparently contradictory clinical, x-ray, and electrocardiographic data, a high incidence of misdiagnosis and ill-advised surgery is likely.

DIAGNOSIS

The diagnosis of acquired mitral stenosis may be difficult, especially in young pa-

*Cardiac index equals cardiac output in liters per minute divided by the body surface area in square meters.

tients lacking a history of a definite rheumatic episode. Awareness that the condition occurs in the pediatric age group coupled with a history of progressive symptoms and the previously described physical findings should suggest the diagnosis. The x-ray, the electrocardiogram, and the phonocardiogram can furnish further information to help in quantitating the severity of the stenotic process.

There should be no difficulty in distinguishing patients with acute rheumatic carditis from those with severe mechanical mitral stenosis. The coexistence of the other signs and symptoms of acute rheumatic fever and the laboratory signs of rheumatic activity are helpful. The physical examination is most important. Patients with mild acute rheumatic carditis may be expected to have only the holosystolic murmur of mitral regurgitation. In those with more severe involvement, pulmonary edema may occur, but it is always associated with striking cardiomegaly. In individuals with severe acute carditis the first sound is soft, and a prominent, often high-pitched, apical murmur of mitral regurgitation is present. This is frequently associated with a loud third sound and a rumbling early diastolic murmur of so-called relative mitral stenosis.

A problem may be posed by children with chronic rheumatic heart disease in whom some degree of mitral narrowing is present but the dominant lesion is mitral regurgitation. These patients can usually be recognized if careful attention is paid to the history, physical examination, and simpler ancillary studies. The acute rheumatic episode tends to be more severe in patients with dominant regurgitation. As mentioned previously, there may be no history of any known acute episode whatever in a large number of patients who develop mitral stenosis. Second, although symptoms of dyspnea on exertion may be present both in the group with mitral regurgitation and in those with tight mitral stenosis, episodes of overt pulmonary edema are virtually confined to those with dominant stenosis, unless there is severe, superimposed active carditis.

The physical examination further aids in distinguishing dominant mitral stenosis from regurgitation. A hyperdynamic left ventricular type of impulse is noted only in patients with significant mitral (or aortic)

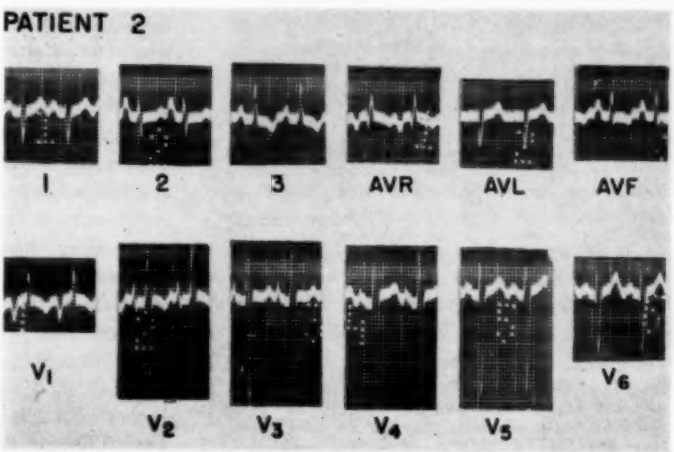


Fig. 10. Patient 2. This 13-year-old patient had tight mitral stenosis and severe pulmonary hypertension (pulmonary artery pressure 75/32). The electrocardiogram suggests right and left atrial enlargement, right axis deviation, and right ventricular hypertrophy.

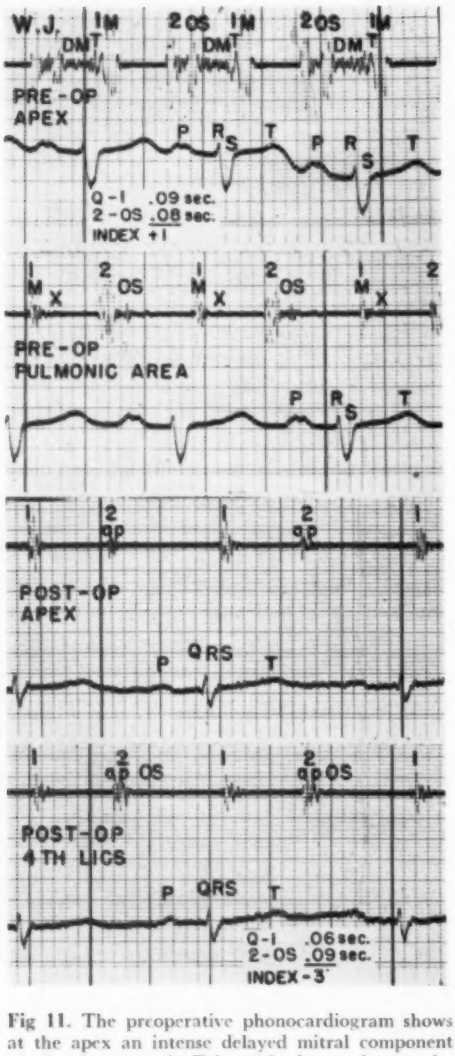


Fig 11. The preoperative phonocardiogram shows at the apex an intense delayed mitral component of the first sound. Tricuspid closure is not delayed and is well shown. No systolic murmur is present. The second sound is quite intense and narrowly split over the pulmonic area. A prominent opening snap (OS) occurs .08 seconds after the onset of the second sound. A low frequency apical diastolic rumble is shown in the brief interval between the opening snap and the next first sound. The phonocardiographic index of +1 suggests a process of at least moderate severity.

The heart sounds become virtually normal postoperatively, the diastolic murmur no longer evident and only a faint opening snap persisting. The postoperative phonocardiographic index of −3 correlates with the improved hemodynamic status. (From Castle and Craige, Pediatrics 26: 511, 1960. By permission of Charles C Thomas, Publisher.)

insufficiency. On auscultation, holosystolic apical murmurs may be present in patients with dominant mitral stenosis. A very soft or absent systolic murmur militates against mitral regurgitation as the major lesion, however. In the presence of pulmonary hypertension, the second sound over the pulmonary area is loud and not clearly split in mitral stenosis. In dominant mitral regurgitation, abnormally wide splitting of the second sound is frequently noted. An opening snap may be present in both groups but is much more consistent in the severe stenosis group. Also, and of great importance, the presence of a third sound highly suggests that stenosis is not hemodynamically significant. In both groups prominent protodiastolic murmurs may be present. However, a lengthy diastolic murmur, especially when associated with a presystolic crescendo, is virtually diagnostic of predominating stenosis.

With reference to the atria, the electrocardiogram is similar in mitral stenosis and insufficiency, revealing left atrial enlargement in each. However, it often differs in respect to ventricular dominance. Right ventricular hypertrophy is common in severe mitral stenosis, whereas left ventricular enlargement usually is seen in patients with dominant regurgitation. Radiographic examination gives further information (see above). Special attention should be paid to the size and contour of the left atrium and to the nature of the pulmonary vasculature. When mitral regurgitation predominates, arterial narrowing is not evident, although pulmonary venous engorgement is frequently noted. It must be emphasized, however, that similar signs of venous engorgement may predominate in children with tight stenosis who have developed little or no reactive pulmonary arterial changes. Last, the phonocardiogram may assist, for in dominant regurgitation both the Q-1 and 2-OS times may be shortened.[48] In severe mitral stenosis the Q-1 time tends to lengthen as the 2-OS time shortens.

In the evaluation of the patient with mi-

tral disease the findings of all clinical and ancillary studies must be considered together. Although some patients fall in a borderline group it usually is possible to distinguish those with tight stenosis from those with dominant mitral regurgitation without recourse to the more dangerous, complicated, and expensive techniques of right and left cardiac catheterization.

Other diseases may give rise to clinical and hemodynamic alterations identical with those of mitral stenosis. Among these are tumors of the left atrium which are rare in childhood. Atypical clinical findings such as embolization without atrial fibrillation or marked positional changes in symptoms and murmurs should alert the physician to this diagnostic possibility.[55] Another rare lesion is cor triatriatum. The great majority of patients with this defect have symptoms from early infancy. In an occasional older child, however, the disease may closely mimic acquired mitral stenosis. In these cases, the preoperative diagnosis may be made with reasonable certainty only if a high pulmonary capillary pressure is recorded at the same time a normal pressure is found in the body of the left atrium.[56]

Individuals with primary pulmonary hypertension may evidence symptoms of progressive dyspnea. However, episodes of pulmonary edema do not occur and there is no evidence of left atrial enlargement on the electrocardiogram or x-ray. Moreover, the two groups differ strikingly with reference to the pulmonary vascular markings. In primary pulmonary hypertension venous congestion is lacking, and diffuse (rather than primarily basilar) arterial oligemia is present. The presence of an opening snap and an apical diastolic rumble tends to exclude primary pulmonary hypertension. However, these auscultatory findings may be absent in an occasional patient with tight mitral stenosis and severe pulmonary hypertension.

From the point of view of auscultation, large atrial septal defect may mimic mitral stenosis. In the former lesion, the right atrium and ventricle are often greatly enlarged and the tricuspid valve may be displaced to the left. A loud (tricuspid) first sound may be mistaken for a loud "M-1" and a diastolic murmur of increased tricuspid flow may be interpreted as a murmur of mitral stenosis. Moreover, in atrial septal defect a tricuspid opening sound rarely is heard. This may be mistaken for a mitral opening snap. Wide, fixed splitting of the second sound and the absence of a presystolic crescendo are usual in atrial septal defects; a presystolic murmur may also be absent in mitral stenosis in the presence of atrial fibrillation. Other aspects of the evaluation of the patient (history, x-ray, and electrocardiogram) usually permit the separation of these diseases.*

Congenital mitral stenosis may be suspected in children with no history of an acute rheumatic episode. While it is true that most children with this condition experience symptoms from infancy, an occasional patient may appear to develop progressive symptoms in later childhood. This subject was recently reviewed by Starkey,[59] who has summarized the various valve types seen in these patients. He mentions that patients with congenital mitral stenosis who survive to 10 or 12 years of age (and hence are apt to be confused with those with an acquired lesion) are likely to have a funnel-shaped valve with fusion of the commissures. These may be amenable to at least partial relief by a standard closed mitral valvulotomy.

THERAPY

Proper case selection for mitral valvulotomy depends primarily on precise diagnosis and on the accurate appraisal of the degree of severity of the mitral block. Surgery is generally indicated in the symptomatic patient with tight mitral stenosis. It is particularly urgent in individuals subject to bouts of pulmonary edema, orthop-

*Acquired mitral stenosis may develop in a patient with an atrial septal defect. This, the so-called Lutembacher syndrome, is briefly reviewed by Edwards.[57] The rarity of this combination is stressed by Nadas and Alimurung.[58]

nea, and paroxysmal dyspnea. The presence of severe reactive pulmonary hypertension, with or without severe symptoms, also is a clear indication for valvulotomy. Wood states that hemoptysis occurring early in the course of mitral stenosis does not call for surgical intervention.[60] However, in view of our experience with Patient 5 who had several bouts of hemoptysis followed by a fatal first episode of pulmonary edema, we do not concur on this point. Operative mortality is higher and a beneficial result is less likely in the patient with congestive failure. Nevertheless, following a course of intensive medical management, operation must be considered in these cases.

In the preceding section, the separation of patients with dominant mitral stenosis from those with predominating mitral regurgitation was discussed. It is very important that patients in the latter category be accurately recognized, for not only are the results of surgery now much less satisfactory in these patients, but also any operative intervention must be attempted via an open technique.

Occasionally mitral valvulotomy may have to be performed as an emergency procedure. In most instances, however, a preoperative period of bed rest and reassurance is advisable. In all cases a low salt diet and digitalis are recommended. The latter serves to protect the patient from an excessive ventricular rate should atrial fibrillation develop postoperatively.[60] In patients who have exhibited embolic phenomena or who have a marked elevation of pulmonary vascular resistance, Wood recommends the use of anticoagulants while the patient awaits operation.

The standard closed mitral valvulotomy has proved a very satisfactory operation, but with the simplification and decreased mortality from "open" procedures, these approaches are coming to be preferred in many institutions. We believe that at present a closed valvulotomy should be planned for the patient with severe mitral stenosis but that facilities should be available at the time of operation so that extracorporeal circulation may be utilized if the surgeon believes an open approach is warranted.

The results of mitral valvulotomy in children have in general been excellent. Symptoms have quickly been ameliorated and a remarkable, prompt improvement in general well-being has followed. In many patients, there is also a striking growth spurt.

Pathologic examination of the surgically removed left atrial appendage frequently demonstrates the presence of Aschoff bodies.[61, 62] These are considered specific for rheumatic heart disease, and they are more commonly found in patients in the younger age groups. Histologic rheumatic lesions may be present despite absence of clinical rheumatic activity.[62] In children with acquired mitral stenosis but without a history of an acute rheumatic episode, atrial biopsy becomes a diagnostic procedure serving to establish the disease to be of rheumatic origin.

In the postoperative period the patient should be followed closely for signs of embolic phenomena. Should these appear, prompt anticoagulant therapy is indicated. Although the effects of cerebral emboli may be temporarily very severe, the outlook for complete or nearly complete recovery is usually very good, especially in these younger patients. It is obvious also that the emotional effects of cerebral embolization are apt to be quite devastating and that intensive psychologic support and reassurance are essential at this time.

In the postoperative period a group of findings originally termed the "postcommissurotomy syndrome" may appear. It is now recognized that this is a nonspecific reaction which may follow any procedure in which the pericardium has been subjected to trauma. Hence, the term traumatic pericarditis is now preferred. This illness is characterized by fever, pericardial pain, general malaise, and occasionally pericardial effusion. Many recurrences over a matter of months to a year or more may develop.[60] The condition ultimately clears but if the reaction is severe, steroid therapy may be warranted. In the average case, however,

salicylates afford ample symptomatic relief.

It has been the practice in our institution to administer quinidine before and after operation in the hope of preventing atrial fibrillation. Nevertheless, there is merit in the suggestion by Wood[18] that this drug be withheld until the third postoperative week at which time an attempt should be made to convert the fibrillation in all cases, whether or not the arrhythmia be of recent onset.[60]

After convalescence from mitral valvulotomy the patient gradually resumes physical activity which probably need not be restricted save for prohibiting vigorous competitive sports. As in any child with rheumatic heart disease, continuous penicillin prophylaxis is essential. In patients who have had a marked elevation in pulmonary vascular resistance, the return to a more nearly normal hemodynamic status is slow. In such instances the period of convalescence should be prolonged, and digitalis, salt restriction, and possibly anticoagulants are required for many months.[60]

The true incidence of re-stenosis will not be known for many years. Wilcken[63a] has recently presented evidence that the risk of re-stenosis depends to a large extent on the adequacy of initial valvulotomy. In Patterson and Marshall's[64] study, 7 out of 400 patients developed recurrences from 8 to 41 months after valvulotomy. It is interesting that at a second operation only one of 5 patients in whom atrial biopsy was performed demonstrated Aschoff bodies. What this means is uncertain but the implication is that an active rheumatic process may not be the only factor in the development of re-stenosis.

CONCLUSION

Acquired critical mitral stenosis may develop in the pediatric age group. The clinical profile is similar to that of adults and the diagnosis can usually be made on the basis of the history and physical examination. We have attempted to emphasize the value of the simpler ancillary studies, especially of those with the phonocardiogram and x-ray, in evaluation of the severity of the stenosis and of the associated pulmonary vascular changes. Cardiac catheterization, although not generally necessary, can furnish further helpful ancillary information in selected patients. Mitral valvulotomy results in striking improvement and may be an emergency lifesaving procedure. Regardless of the patient's age, once a diagnosis of tight mitral stenosis is made, consideration of surgery is mandatory.

We are indebted to Dr. C. Glenn Sawyer of the North Carolina Baptist Hospital for furnishing catheterization and clinical data on Patient 3. We also gratefully acknowledge the helpful suggestions of Dr. Ernest Craige, Dr. Thomas Gibson, and Dr. Herbert Harned of the North Carolina Memorial Hospital.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

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THIS white girl was born after a 38 weeks' gestation to a 28-year-old gravida i, para 0, mother. The baby's mother had enjoyed good physical health, but had always been obese and quite nervous. During her pregnancy, she had taken an unknown quantity and variety of medication, available at her place of employment, including Compazine, Dexedrine (10 mg.) and thyroid (1 grain) daily. The last dose of Compazine was taken approximately 6 hours prior to delivery. Delivery was accomplished under spinal anesthesia without difficulty, following 7 hours of active labor. A true knot was found in the pulsating cord. The cord was 70 cm. in length. The placenta was normal in weight and dimensions. There was a yellowish small marginal infarct. The baby's respirations were normally established in less than a minute after birth; only pharyngeal suctioning was employed. Birth weight was 6 pounds, 6 ounces.

The baby was considered abnormal from birth because, although she was alert, she exhibited episodic, sudden, gross, jerking movements of the extremities, head, and jaw, either singly or repetitively, about 10 per minute. There was no peroneal or Chvostek sign. Percussion of muscle showed no abnormal irritability. The child was usually found lying in a frog position, flaccid, and responding to tactile stimulation with a myoclonic jerk. The Moro response was present. The pupils reacted to light, and shining a light into the eyes elicited a blink. The retinas were normal. The deep tendon reflexes were brisk, and the plantar responses equivocal.

Lumbar puncture on the third day of life revealed "CSF pressure definitely not increased," spinal fluid reducing substance 39 mg. per cent, no white cells, and a slightly bloody fluid which progressively cleared during flow. The final sample was xanthochromic. Protein was not determined. A simultaneous blood sugar determination was 45 mg. per cent. Urinalysis was normal. Hematocrit was 41 per cent, and serum calcium was 9.35 mg. per cent. Slight jaundice, suspected the day after birth, persisted 7 days; bilirubin was 15.2 mg. per cent total, with 13.5 mg. per cent indirect on the fourth day of life. Skull films showed a somewhat small cranial vault. There were no intracranial calcifications or abnormalities of the sutures. The electroencephalogram was interpreted as containing a good deal of movement artifact but no abnormalities.

The patient was first seen in the out-

patient department of the Children's Hospital Medical Center at the age of 8 days. The involuntary movements were much less, being apparent only when she was stimulated or when she cried. The circumference of the head was 30.5 cm. She was started upon elixir of phenobarbital (24 mg. daily) and Dilantin (75 mg. daily), after the appearance of frank clonic convulsions of 2 to 3 minutes' duration.

At 3 months of age, the involuntary movements were less but were present particularly when the child was being bathed or dressed. The head circumference was 36.4 cm. The baby was hypertonic and extremely jittery to a hand clap. The arms were flexed at the elbows and the fists were tightly clenched. The reflexes were markedly hyperactive. Clonus was observed. The plantars showed flexor response.

At the age of 3½ months when the baby developed an upper respiratory infection, the seizures were severe, occurring every half hour. The anticonvulsant medication was increased. At the age of 4 months, the head circumference was 37.3 cm. She could not support her head, and she did not smile. Spasticity and hyperactive reflexes were observed. The plantar reflexes were still flexed.

At the age of 5 months, she was admitted for study of the persistence of abnormalities. The father (39 years old) is well. A maternal uncle, as well as a second cousin, had seizures in childhood.

Physical examination showed that the pulse rate was 80 per minute; length, 71 cm.; head circumference, 38.5 cm. (lower 10 per cent); weight, 12 pounds, 12 ounces.

This small female infant was uninterested in her environment. General physical examination was not remarkable. Neurological examination showed no voluntary activity. The baby could not hold her head up when supported in a sitting position. She did not reach or follow a light, and only occasionally blinked at a bright light. Pupils reacted to light and were equal. Rotation of the infant did not result in nystagmus.

The baby was hypotonic when relaxed, but upon stimulation would develop marked hypertonicity to such an extent that extension of the elbows gave a clasp-knife response. She could move all extremities. She was repeatedly seized by gross myoclonic jerks of the four limbs and the head, occasionally while at rest, but especially following tactile stimulation. The arms were flexed and the fists clenched. Her response to pain was normal. Moro and rooting responses were present. Deep tendon reflexes were equally hyperactive with ankle and patellar clonus bilaterally, and extensor plantar responses bilaterally.

Urinalysis was negative. Examination for metachromatic bodies and ferric chloride tests were normal. The cerebrospinal fluid contained protein, 38.4 mg. per cent and 1 white blood cell. An electroencephalogram showed scattered spikes predominantly in the occipital areas.

The baby fed poorly and continued to have repetitive myoclonus as well as longer periods of clonic movements of several minutes, occasionally with the head and eyes deviated to the right and followed by loss of consciousness. Lumbar puncture revealed clear fluid and a "slow flow" through a No. 20 needle. Skull films revealed the cranial vault to be small in comparison with the facial bones. All sutures were present and open, suggesting microcrania, secondary to microcephaly. The patient was discharged on anticonvulsant drugs.

The patient did poorly at home, continuing to have at least one generalized seizure per day, and practically continuous myoclonic jerks of the limbs.

The feeding problem became more severe and she developed progressive weakness. She was found dead in bed shortly before her first birthday.

DR. MAURICE VICTOR.* We are presented with an infant who had serious neurological deficits from the time of birth. Throughout her 1 year of life she was afflicted with myoclonus as well as generalized convulsive seizures. General development was not nor-

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mal and she failed to attain any of the usual motor and behavioral landmarks of the first year of life. The fact that the pupils reacted to light despite the inability to see would point to a cortical basis for the blindness. The abnormal posture of the upper limbs, with the clenched fists, and the arms flexed at the elbows, indicates the presence of bilateral corticospinal tract involvement. The electroencephalographic abnormality, taking the form of a diffuse spiking activity, can be interpreted only as evidence of cerebrocortical disease. The cranial vault was small but, in view of the x-ray findings, this was clearly secondary to the smallness of the brain.

Any formulation of this illness must take into account not only these positive features, but also a number of negative ones. The parents were free of any neurological disease but the familial aspect could not be assessed, since the patient was an only child. Apart from a possible history of drug ingestion, the gestation and birth were normal. Cerebral trauma or anoxia and kernicterus seemed not to be operative in this case. The spinal fluid showed no evidence of inflammatory disease; the mild xanthochromia which was present on the third day of life is a commonplace and probably insignificant finding. Other laboratory examinations ruled out phenylpyruvic oligophrenia and possibly metachromatic leukoencephalopathy as well.

The most arresting clinical feature in this case was obviously the movement abnormality, and it may provide the clue to the diagnosis. As the film strip has shown, the movement abnormality consisted of involuntary repetitive contractions, clonic and shocklike in nature. The contractions were somewhat irregular in amplitude and rhythm and were asynchronous or asymmetrical. The contractions were of sufficient intensity to displace the limb or part of the limb. The abnormal movements occurred when the child was in repose and presumably were obliterated when she was asleep. They were definitely made worse by any stimulation of the part, or perhaps by attempted voluntary movement. To this clinical phenomenon, the name "myoclonus" or "myoclonic jerks" is given; this term deserves further comment.

Myoclonus can be roughly divided into two major categories: the first is so-called palatal myoclonus which is a movement disorder affecting not only the palate, but at times the tongue, lips, diaphragm, and pharynx, and even the upper limbs. The movement of the affected muscles is rhythmic, rather slow, about 30 to 60 per minute, and does not cease during sleep. This disorder can consistently be related to a lesion in the brain stem, more specifically, the central tegmental tract and its immediate connections. Although this disorder is designated as myoclonus by virtue of common neurological usage, it is a unique phenomenon and entirely distinct from all other types of myoclonus.

The second and more common type of myoclonus is random in character rather than rhythmical and is the type with which our patient was afflicted. This type of myoclonus is usually, although not always, associated with epilepsy, so that it may be referred to as myoclonic epilepsy. The term myoclonic epilepsy comprises a diverse group of neurological illnesses, some of which are benign and some of which are associated with intellectual deterioration and other serious abnormalities of the central nervous system. The most common type of myoclonus is the occasional twitch which occurs in persons with idiopathic epilepsy. Such a patient may complain of a few brief clonic contractions of the limb, usually occurring in the morning and of such violence that a shaving brush, for example, may be flung out of the hand; or the twitching may be very frequent over several days and actually culminate in an ordinary convulsive attack. Dementia is usually not a part of this type of myoclonic epilepsy, but it is a prominent feature of a special variety of epilepsy in children, namely, massive myoclonus or jackknife seizures. Another category of myoclonic epilepsy is the one associated with dementia and other signs of progressive neurological disease. The first of these to be adequately described was the familial variety of Unver-

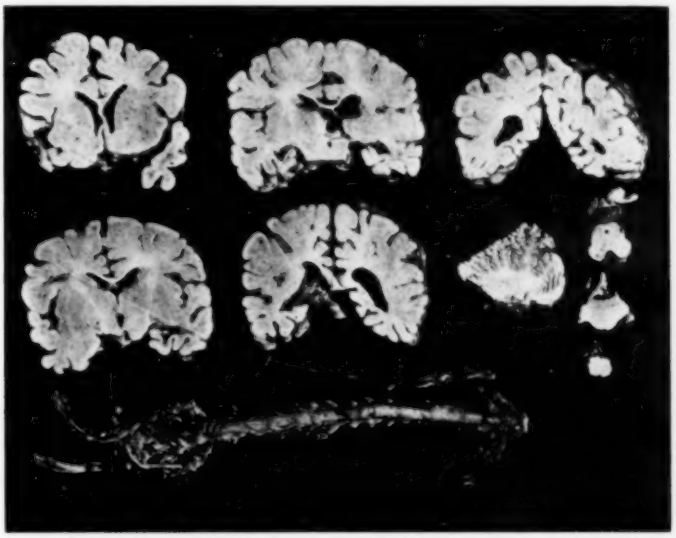

Fig. 1. The central gray matter is well developed; there is relatively little white matter in the centrum semiovale, and primary and secondary convolutions are seen in the cortex.

richt and Lundborg.[1, 2] The outstanding feature of this disorder is the remarkable sensitivity of the myoclonus to stimuli of all sorts. If, for example, a limb is passively displaced, the resulting myoclonic jerk may lead, by a series of incrementally enlarging jerks, to a generalized convulsive seizure. This type of myoclonus is usually a manifestation of the juvenile form of amaurotic family idiocy and is characterized, in addition to the myoclonus, by the presence of seizures, dementia, rigidity, and quadriplegia. Occasionally this familial, stimulus-sensitive myoclonus is associated with a more restricted pathologic change, namely, a curious basophilic inclusion in the cells of the cerebellum, the so-called Lafora inclusion body.

Quite distinct from familial myoclonus is a sporadic type, and again several different entities can be recognized. In adults there occurs a unique subacute illness characterized by dementia, disturbances of gait and coordination, all manner of mental aberration, rigidity, and myoclonus. This is referred to as Jakob-Creutzfeldt disease, and is characterized pathologically by a progressive destruction of the nerve cells of the cerebral and cerebellar cortex. There are now a number of reports of an analogous disease in infants.[3-5] On a background of normal birth and normal early development there occurs a progressive deterioration of the mental faculties, spastic quadriplegia, seizures, myoclonus, and blindness. Here, too, the fundamental pathologic alteration is a destruction of nerve cells in the cerebral mantle with replacement gliosis. Other diseases such as acute and subacute inclusion cell encephalitis may result in a similar clinical picture. Here again one encounters a diffuse disease of the cortical neurons and to a lesser extent of the nerve cells of the basal ganglia and brain stem.

The term myoclonus has been used in relation to several other obscure disorders of the nervous system, as, for example, the paramyclonus multiplex of Friedreich[6] and the dyssynergia cerebellaris myoclonica of Ramsay Hunt.[7] Little need be said about these, since they were purely clinical descriptions and even these have grown dim over the years, so there is disagreement as to what has been described.

Can one possibly relate any of the known

myoclonic dementias to the case under consideration? The presence of symptoms at birth and the lack of progression in our case would seem to make it unique and to separate it from the myoclonic dementias just described. In those, the symptoms occurred on a background of normal development and were clearly progressive in nature. Pathologically, the myoclonic dementias do have one feature in common, namely, a diffuse primary degeneration of nerve cells, particularly of the cerebral and cerebellar cortex. One may argue by analogy that the combination of myoclonic dementia and spastic quadriplegia in our patient had a similar pathologic basis; the diffuse spiking activity in the electroencepalogram would support this contention and the microcephaly would be an acceptable secondary defect. There were no segmental brain stem signs in our case, except for the finding relating to nystagmus, and this is difficult to interpret in the face of so much disease of the cortical neurons. The fact that the major manifestations of this disease were already present at birth, and that no new signs were added, would indicate that the etiological agent acted during fetal life and that its destructive effect on the cortical neurons was largely accomplished during this period.

The precise etiological agent cannot be stated with certainty, but for various reasons it was probably of toxic or of metabolic origin. Compazine toxicity is an interesting consideration, but it cannot be proved or disproved at this time. It is a fact that Compazine may produce serious neurotoxic effects in humans, mainly those of rigidity and dystonia. Damage to neuronal elements has been reported in Compazine-intoxicated animals, but not in their fetuses—at least, not to my knowledge. But in this connection we note that the patient's mother received several medications during her pregnancy, something that seldom happens in laboratory experiments on animals.

I would conclude that we are dealing here with an instance of widespread neuronal degeneration affecting the cerebrocortical mantle. At least, this is the type of pathologic change which characterizes analogous types of myoclonic dementia. We do not have clear evidence of brain stem disease. The disease struck in fetal life, and its precise etiology

Fig. 2. There is a very haphazard arrangement of nerve cells in the cortex, as well as a prominent increase in number of protoplasmic astrocytes. (Hematoxylin and eosin. Original magnification ×150.)

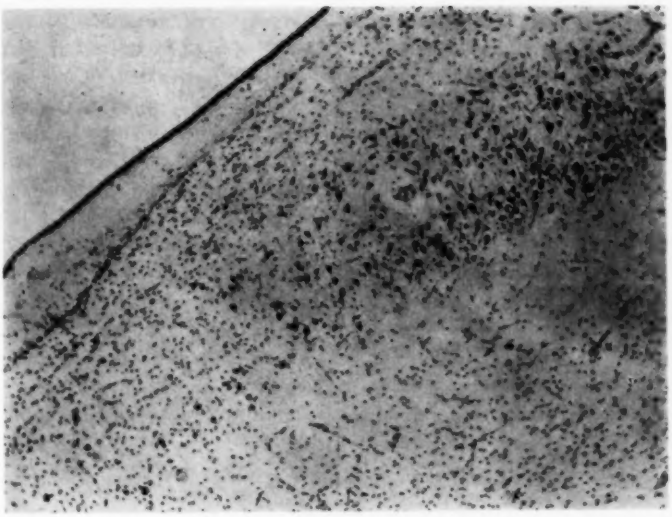

Fig. 3. In Sommer's sector of the hippocampus there is a striking diminution in the number of nerve cells, as well as a mild glial replacement. (Hematoxylin and eosin. Original magnification ×150.)

is unknown to me, but I would surmise that it was metabolic or toxic in nature and not related to trauma, tumor, kernicterus, or inflammatory disease.

Dr. Randolph K. Byers. There is one misleading statement in the protocol. Although there was no nystagmus when the baby was taken up and rotated, there was deviation of the eyes.

Dr. Victor. This would suggest that some impulses were getting through from the vestibular nuclei to the conjugate gaze centers. I cannot explain the absence of nystagmus, unless it was due to an absence of the optical-kinetic response which in turn was due to disease of the parietooccipital cortex.

Dr. Richmond S. Paine. I saw this child several times after the first week of life. I have seen 4 babies with similar myoclonic movements occurring mostly in response to stimuli of almost any sort, whether exposure to manipulation, light, handclap, or something else, in the newborn period. One other of the 4 has a history of a true knot in the umbilical cord, whatever that may or may not be worth. Another one has a history of anoxia at birth. Some students of neurology in the newborn, particularly Prechtal,[8] believe that this type of hyperkinesis is characteristic of response to anoxic birth. He maintains that most of these will perhaps turn out to have athetotic cerebral palsies later on. I should have thought that they were about as likely to be spastic as to be athetotic. Movement of this sort also occurs in some metabolic defects, particularly the disease which Mencke described from this hospital some years ago in which the urine smells of maple syrup and contains branched chain amino acids. I am still following another baby, who had a sibling with similar movements, both of them moving just about like this baby, but nothing abnormal could be identified in the urine. The autopsy on the sibling was rather unrevealing, so that it appears that this type of motion may have more than one cause, perhaps anoxic, perhaps metabolic, perhaps a prenatal cerebral defect. Also occasionally one sees an early movement disorder in a subsequently normal child. In the present case the small size of the head suggests intrauterine onset.

Dr. Gordon F. Vawter. Dr. Paine, were

any of these other children you mentioned microcephalic at birth?

Dr. Paine. No, I do not believe any of the others were.

Dr. Byers. We see a great many babies who come in with the story of what is called seizures or fits, which actually indicate myoclonus. In practically every one of them the mother says that the baby was reaching for things at 3, 4, or 5 months or something like that, and then dementia takes place. This is a very common syndrome in babies. I think we have seen as many as 6 a month, often coming in with so-called "salaam seizures," but they all turn out eventually to be microcephalic, if they are not microcephalic already. We have very little information on these children since they live on for long times. It is a very common syndrome and occasionally goes on over to grand mal seizures too. Today's patient, however, is unlike these others in that the abnormality was apparent at birth.

Dr. Vawter. Does anyone want to comment further upon the drugs this mother received?

Dr. Clement A. Smith. We all know that a number of women receiving Compazine have been delivered at the Boston Lying-in Hospital, as well as many in other institutions, with absolutely no adverse effects upon the fetus so far as we are now aware. However, we are always suspicious of the effects of drugs when we are faced with unusual clinical situations, such as this infant presented. This therapy, which included tranquilizers such as Compazine, seemed one of the few clues we had, even though the drug was stopped a few hours before delivery. It seemed possible that we might have been dealing with an unusual dose of a drug for which comparable experience is hard to come by. We know that Compazine competes for glucuronide in the liver and suspect, in view of the occasional mental and motor complications of tranquilizers in older children and adults, that such drugs may compete in other systems too. Although the movement defect observed here was not characteristic, we even tried more or less empirically the type of treatment we use in suspected pyridoxin dependency states, with negative effects.

Dr. Paine. Since Dr. Murray Pendleton and I have been studying the effect of rotational vestibular stimulation in newborn infants, we might comment upon the lack of nystagmus here. Briefly, we find that this response may be lost under a variety of circumstances, wherein one expects cerebral depression, as in babies of heavily anesthetized mothers, of diabetic mothers, after postanoxic births, and in the presence of deep jaundice. It is difficult to be sure how specifically one should interpret this finding in terms of areas of central nervous system localization.

Dr. Vawter. Dr. Banker will present the findings.

Dr. Betty Q. Banker. At death the height was in the fiftieth percentile whereas the weight was below the third percentile. Chronic bronchitis, congestion, and terminal aspiration were found in the lungs. No other important anatomic lesions are found in the viscera.

The rather small head measured 39 cm. in circumference and the brain weighed 350 Gm. as compared to 850 Gm. expected for the child's age. Coronal sections (Fig. 1) show that there is a quite well-formed cerebral hemisphere with primary and secondary sulci, moderately enlarged ventricular system, and prominent cerebellar folia suggesting focal change. Note the unusually delicate and thin corpus callosum, indicating decrease in the number of crossing fibers.

Microscopically, most prominent are diffuse neuronal changes (Fig. 2) with decrease in number and disarrangement of the normal columnlike pattern coupled with replacement gliosis characterized by increase in microglia and astrocytes. These irregular areas of damage are especially prominent in the depths of the cerebral sulci (Fig. 2), hippocampal area (Fig. 3), Purkinje cells, and dentate nuclei. These are sites which are particularly susceptible to metabolic injury. Ectopic neurons in white matter suggest intrauterine developmental failure of migration. In white matter there is extensive is-

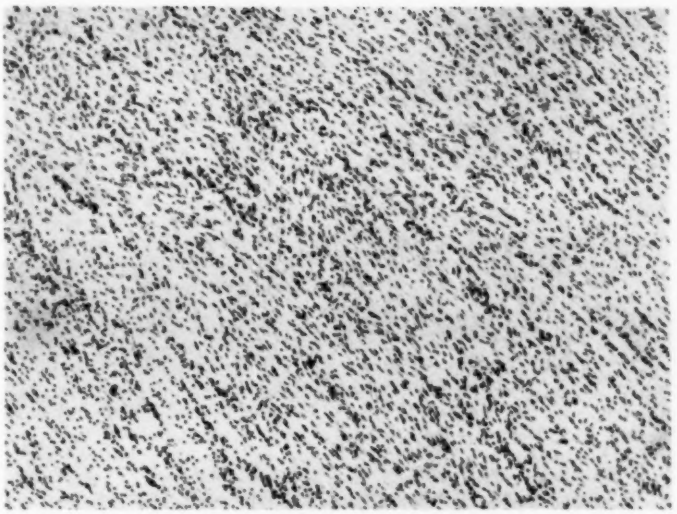

Fig. 4. There are many ectopic nerve cells in the deep white matter. In addition, there is an isomorphic gliosis in which the astrocytes are increased in number and are traveling in the same direction. This change represents a tract degeneration. (Hematoxylin and eosin. Original magnification ×135.)

morphic gliosis indicating secondary tract disease rather than primary injury of white matter (Fig. 4). Associated with this is a lack of the normal myelinization. There was a mild neuronal loss in the thalamus and nuclei of the basal ganglia. There was also a prominent astrocytic hyperplasia in these nuclei.

The changes appear to be of one age and therefore do not appear to be progressive. The stage of development suggests injury in the third trimester. There are several conditions which may lead to a related picture: hypoglycemia of which we have no history, hyperthermia, which, unlike today's case, usually produces more severe cerebellar injury than cerebral and hepatic encephalopathy, although this seldom is accompanied by such deficiency in neuron population. However, histologically the liver is normal. The last of such possible etiological agents that I shall mention is anoxia, and the changes here certainly could fit very well, particularly if they were to develop a month or so postnatally. Dr. Larroche and I have recently been very much interested in another type of lesion, not seen in this child, which we believe may be at least partly associated with perinatal anoxia. This is the focal necrosis in the paraventricular white matter of the cerebral hemispheres. The lack of evidence of such changes in the present case raises doubt in our minds as to whether anoxia is responsible for the changes seen in this case.

Therefore, we too questioned the role of the maternal drug intake. Dr. Leon Z. Saunders of Smith Kline & French states that they were able to give 9.8 mg. of Compazine per kilogram body weight to pregnant rats daily with no apparent adverse effect upon the mother or the litter in any way: the conclusion is drawn that Compazine does not cross the rat placental barrier at all or, if so, only in minute quantities.

Pathologic studies in human cases in which rigidity and involuntary movements complicate tranquilizer therapy are meager, partly, one supposes, because the effects of the drugs are transient. I would summarize such a few studies[8-11] as presenting changes, if any, which remain to me quite controversial. Moreover, similar clinical and pathologic findings were not found in 2 infants whose

mothers received 30 mg. of Compazine twice daily throughout pregnancy. On the other hand we have seen 2 other infants whose myoclonus dated from birth. The pathologic findings were essentially identical with those of this child. In both of these infants, however, there is no history of Compazine or tranquilizer ingestion, and we have no clear idea as to the etiology of the pathologic changes.

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COMMENTS ON CURRENT LITERATURE

Rabies infection transmitted by insectivorous bats: Human case with virus isolation from spinal fluid during life

THE relationship between rabies infection and vampire bats has been recognized in South and Central America for many years. Epizootics of a paralyzing fatal disease in livestock were described as early as 1910-1911. Negri bodies observed in the brains of cattle dying of this paralytic disease identified the infection as rabies,[1] and transmission of the virus by the hematophagous bat, an exclusive blood feeder, was surmised on the basis of observations by ranchmen. Somewhat later (1916) rabies virus was recovered from the brain of a vampire bat captured in Brazil[2] while feeding on cattle during the day. Further investigation verified the impression that the virus of rabies was transmitted to cattle and other livestock by the bite of blood-feeding bats. The occurrence of over 50 cases of rabies in human beings coincidentally with an epizootic of paralyzing disease of cattle in Trinidad in 1925 suggested an association between the animal and the human infection. Virus was isolated from brain tissue and from the salivary glands of vampire bats in this area.[3] In connection with a similar outbreak of livestock disease in Mexico in 1944, the virus of rabies was recovered from brain tissue of cattle, and from the brain, salivary glands, and saliva of vampire bats.[4] Comparable observations were made in Honduras.[4]

While in early investigations an occasional fruit-eating or insectivorous bat was found to be infected, it is only within recent years that the importance of these bats in the epidemiology of rabies in human beings has been appreciated. Recognition of this hazard is of great importance in the United States and Canada where the insectivorous bats are abundant, the vampire and fructivorous bats being found only rarely, and those few in states bordering on Mexico. The first case of rabies thought to have resulted from the bite of an insectivorous bat was probably that described by Sulkin and Greve.[5] This occurred in a 43-year-old woman who was transferred from West Texas to a Dallas hospital with symptoms and findings suggestive of bulbar poliomyelitis. Inquiry into the immediate history revealed that 3 weeks before admission to the hospital, and about 16 days before onset of her illness, the patient had investigated what appeared to be a dead bat. The animal proved to be alive, and the woman was bitten on the left forearm. No particular ill effects were experienced from the bite for about 16 days when the patient began to complain of aching in the left arm,

and developed fever (103° F.). The fever continued accompanied by nausea, vomiting, generalized aching, and inability to move the left arm. As difficulty in swallowing secretions increased, the patient was transferred to Dallas with the tentative diagnosis of bulbar poliomyelitis. Lumbar puncture revealed 24 cells and spinal fluid protein of 74 mg. per cent. The patient's course deteriorated steadily, and death occurred 25 days following the bat bite. Postmortem examination revealed "encephalitis with demonstrable Negri bodies in central motor neurons compatible with rabies."[5] Unfortunately, the bat was not available for identification and study; however, the sequence of events and the clinical course in this patient together with the autopsy findings strongly suggested the bat bite as the source of the rabies infection.

About the same time rabies virus was isolated from cave-dwelling bats in Texas, and within a period of one year (1953-1954) 5 other persons, 4 of whom were children, were bitten by rabid nonvampire bats in Texas.[6, 7] All of these attacks were provoked by the handling of resting or obviously sick bats. The isolation of rabies virus from the brain of a yellow bat captured in Florida in 1953 following an unprovoked daylight attack on a 7-year-old boy established the fact that insectivorous, free-living noncolonial bats do harbor the infection.[8] The boy received prompt medical attention, including rabies immunization, and made a complete recovery. Further investigation resulted in the successful isolation of virus from 6 of 208 apparently normal insectivorous, noncolonial bats captured within a radius of 25 to 30 miles of the initial positive specimen. Somewhat later in the same year, a woman in Boiling Springs, Pennsylvania,[9] experienced an unprovoked attack by a bat and was bitten on the upper arm. Both touch preparations and sections of the bat's brain revealed typical Negri bodies, and inoculation of rabbits with brain tissue from this bat resulted in manifestations of rabies within 24 to 27 days following inoculation. The woman who was bitten had prompt medical care, received antirabies prophylaxis, and did not develop rabies. Subsequently the bat in this instance was identified as the hoary bat, an insectivorous species that is widely distributed over the United States and Canada, especially during the summer months.

More recently, transmission of rabies from a naturally infected insectivorous bat to a human subject by bite was verified by the isolation and identification of virus from brain tissue of both the biting bat and the human victim.[10] Another case of note is that of an epidemiologist and entomologist who died in Texas in 1956 after having spent more than a year in investigative work with bats and bat rabies.[6, 11] While the route of infection in this instance was not known, his work provided ample opportunity for exposure, including exploration of the caves in Texas, from some of which bat-rabies isolations had been accomplished. It was suggested that he might have acquired the infection through a chronic skin eruption on his neck by accidentally rubbing bat guano or saliva from his glove across this chronically irritated area. This man's illness was characterized by convulsions, inability to swallow, and respiratory difficulty. Negri bodies were found in the brain at necropsy, and animal inoculation studies confirmed the diagnosis of rabies. In a number of laboratories experimental infection of insectivorous bats with rabies virus has been accomplished, the presence of virus has been demonstrated in the salivary glands and saliva of these bats, and naturally infected insectivorous bats have been known to transmit the disease to other mammals by bite.[6, 11, 12]

A case of rabies in a human subject, presumably transmitted by the bite of a bat, is described by Kent and Finegold[13] in a recent issue of the *New England Journal of Medicine*. The virus of rabies was isolated from a spinal fluid specimen obtained during life, as well as from brain tissue taken at autopsy. The patient was a 53-year-old man who was admitted to a Veterans Administration Hospital on June 1, 1959, with the chief com-

plaints of shortness of breath and retching of recent onset. The initial manifestations which were suggestive of myocardial infarction had led to hospital referral by a private physician. Inquiry into the patient's activities revealed that from April 9 to May 1 he was investigating caves in Texas and Mexico as possible sources of commercial guano. A companion noted that on one occasion during the investigations this man had blood on his face either from a scratch or from a minor bite, although at the time and later the patient denied being bitten. The companion also stated that at some locations thousands of disturbed bats flew past them. No other exposure to rabies could be elicited on subsequent inquiry. Tenderness of the left arm and retrosternal pain were noted from about May 23, progressing to numbness of the left side. Just previous to this the patient had experienced a short period of nausea, vomiting, and diarrhea. Late in the day on May 30 numbness of the left side, retrosternal pain, and nausea caused him to seek the advice of a physician who referred him to the hospital. While the general physical examination on admission disclosed nothing remarkable, the patient was extremely restless and appeared somewhat dyspneic. The retching was periodic and at times became violent. At this time the blood count was unremarkable; the serum creatinine was 1.7 mg. per cent; urinalysis was within normal limits, except for a specific gravity finding of 1.035, a 1 plus test for protein, a 1 plus test for sugar, and a 4 plus test for acetone. On two separate occasions during the brief hospitalization period the sedimentation rate was reported as low. Chest x-ray was described as negative, and an electrocardiogram showed sinus bradycardia with occasional premature atrial and ventricular contractions. A spinal fluid sample obtained at this time was clear and contained 4 lymphocytes per cubic millimeter.

Following admission to the hospital the patient became progressively more restless, confused, and disoriented, with spells of retching and rapid labored breathing, controlled only by the intravenous administration of sedatives. All liquids by mouth were refused; a few hours before death excessive salivation and foaming at the mouth were noted. Negri bodies were observed in brain tissue taken at necropsy, and the diagnosis of rabies was confirmed by animal inoculation studies, and by serum neutralization tests identifying the rabies virus. Rabies virus was isolated also from a specimen of spinal fluid obtained during life.

Initially this patient presented a diagnostic problem, particularly before details on cave visits and possible bat exposure were available, having been admitted first to the cardiac service with a tentative diagnosis of myocardial infarction. The brief episode of diarrhea 10 days before admission, the visit to Mexico, and the relative bradycardia with electrocardiographic changes focused attention on the possibility of typhoid fever; for this reason the patient was treated intravenously with chloramphenicol. While there was no positive evidence of exposure, it was apparent clinically by the end of the second day that the patient was suffering from rabies.

In a discussion of this case the authors[13] take the opportunity to emphasize certain aspects of rabies infection. The early symptom of numbness and tenderness in one extremity or region following the bite of a potentially rabid animal is very suggestive of the diagnosis of rabies, was stressed early by Pawan[3] as a reliable finding in the experiences in Trinidad, and has been reported frequently in the literature. The bradycardia, likewise, is considered characteristic, and has been described in experimental rabies infection in dogs. The glycosuria, acetonuria, leukocytosis, and the lack of spinal fluid findings in their patient are considered by the authors to be typical of rabies infection; they consider the low sedimentation rate observed on two occasions to be noteworthy. The presence of rabies virus in the cerebrospinal fluid has been detected in a few instances only, perhaps because specimens are not always available for investigation. The authors[13] have been im-

pressed by the reported use of fluorescein-antibody staining techniques as a means of demonstrating rabies virus in brain tissue and salivary glands, suggesting that these techniques might be adapted to examination of spinal fluid and saliva for early diagnosis of rabies. However, as is indicated by a recent report in the *American Journal of Public Health* (November, 1960),[14] these procedures as applied to virus detection have certain limitations which are currently under study. Kent and Finegold[13] state that in their case the diagnosis could not have been made with certainty in the absence of viral studies, and that such studies assume greater importance when one considers that in only about 40 per cent of the patients with rabies studied have Negri bodies been demonstrated in the brain at autopsy.

In summary, the authors emphasize the widespread distribution of rabies virus among insectivorous bats in this country and in Canada, the virus of rabies having been isolated from insectivorous bats in 24 states, with comparable distribution reported from Canada, and that anyone bitten or otherwise definitely exposed should be treated for rabies according to the established principles outlined by the World Health Organization.[15] While the majority of the victims have exposed themselves unnecessarily through the careless handling of resting or obviously sick bats, a few cases of unprovoked attack have occurred. Both exposure hazards are of importance in the pediatric age group.

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PEDIATRIC PROFILES

Bronson Crothers

(1884–1959)

BRONSON CROTHERS, winner of the American Pediatric Society's John Howland Award for 1960, lived to know of his honor, but did not survive to receive it. He was greatly gratified and characteristically surprised that he should have been chosen. "I can't see why they did it" was a phrase often repeated in thinking and talking about it in the last two months of his life.

Our purpose today is to attempt documentation of the reasons for his selection. Simply stated, he was chosen by the Society because he was one of the major contributors to the pediatrics of his era. His success was born of a lively intelligence, motivated by a need to be of service to his fellow men. Doubtless the inspiration of his father, the Reverend Samuel McCord Crothers, who in the 1870's had taken religious care of such violent parts of the young West as Virginia City, Nevada, and of remote places such as Santa Barbara, California, had fostered this need.

Bronson was born in Elmira, New York, on July 10, 1884, and spent most of his boyhood in St. Paul, Minnesota, where his father was minister for some years before moving to Cambridge, Massachusetts. Bronson was fond of telling of the many Sunday night suppers "for all comers," usually featuring escalloped oysters, frequently stretched by the addition of crackers as the need arose. He maintained that his personal acquaintance with oysters was slight.

He was graduated from Harvard College in 1904, and from Harvard Medical School in 1909, and afterward served as house pupil at the Massachusetts General Hospital, where the skill and acumen of Dr. Frederick Shattuck did much to orient him toward the personal side of medicine. He continued his training as intern at the Children's Hospital in Boston where he was a contemporary of Dr. James Gamble and Dr. Frederick Tisdall.

A trial of private practice of pediatrics in St. Paul convinced him that his role in life was not that of a private practitioner, and he joined the British Army Medical Corps in the Massachusetts General Hospital Unit in 1915 as a Major. Though he found marching his command through a given archway at a prearranged time virtually impossible, he did find a chance to be of service to men in need and this gave him compensatory satisfaction. He brought back many anecdotes that tickled his fancy; for example, when morale was running low, and there was some murmuring in the ranks, officers in general had been instructed to see to it that enlisted men were assiduous in saluting. About a hospital one day he came upon a group of lounging orderlies who paid him no heed.

"Don't you salute officers?" he asked.

"Indeed we do, Govner," was the to him rewarding reply, "but we thought you was a doctor."

As an aftermath of his service he was "mentioned in despatches":

The War of 1914-1918
Royal Army Medical Corps
The Hon. Major B. Crothers
Was mentioned in a despatch from
Field Marshall Sir Douglas Haig, K.J.,
K.T., K.B., Q.M., G.C.V.O., K.C.I.E.,
Dated 16th March 1919
for gallant and distinguished Services in the Field.
I have it on Command from the King
to record His Majesty's
High appreciation of the Services rendered.
Winston S. Churchill,
Secretary of State for War.
Whitehall S. W.
1st July, 1919

Never did he mention this to anyone, or discuss the reason for it.

In 1917, upon the entry of the United States into the war, he returned to this country and was commissioned in the United States Army Medical Corps. During this interval he married Alice Ames of St. Paul, whom he had known since childhood.

During his service in the British Army he developed great admiration for the neurological acumen and perceptive directness of many of the British medical officers with whom he was associated. On the lighter side he was tickled to remember such exchanges as that between Sir Almoth Wright and a plump General whom Bronson found somewhat obsessive. The General was inveighing to Sir Almoth and Bronson against the insubordination of medical officers, and when Sir Almoth had had his fill he turned on his tormentor with the remark, "One pinprick, General, and poof! nothing there."

On the serious side, Bronson was greatly impressed by the careful observations of Sir Henry Head and Dr. George Riddoch on war wounds of the nervous system and particulary those affecting the spinal cord. On his return to civilian life he devoted himself to study of the nervous system for a year in the laboratory of Dr. Walter Cannon under the guidance of Dr. Stanley Cobb, and at the Neurological Institute in New York with Dr. Frederick Tilney.

He was permitted to proceed with his interest in the fall of 1920 when "at a meeting of the Visiting Staff of the Children's Hospital, held at the Harvard Club at 6 P.M., October 1st, 1920, at which Drs. Ernst, Folin, Hunt, Wolbach, Stone and Morse were present, it was voted to nominate Dr. Bronson Crothers for the position of Neurologist to the hospital."

Thus began his career as one of the pioneers of pediatric neurology. For the next thirty-eight years he was extremely active at the Children's Hospital both in its service and in that of the Harvard Medical School where he became Clinical Professor of Pediatrics in 1945. Even after his retirement to Emeritus status in 1952 he continued to devote most of his time to a follow-up study of the large number of patients suffering from cerebral palsy whom he had seen.

Fig. 1.

On taking up his new duties, it soon became apparent to him that the talents and training of one man were inadequate to the task of caring for the diverse group of cases that came his way. Referrals of intellectual and emotional problems to neighboring psychologists and psychiatrists seldom accomplished much. It was clear to him that an integrated group consisting of people interested in objectively definable neurological and psychologic aberrations could contribute substantially to the clarification of such poorly understood syndromes as cerebral palsy, behavior problems, and learning difficulties.

Reference to a collected list of his publications shows that during these earlier years of his stewardship his contributions dealt in large measure with structural changes in the nervous system of infants and young children. His first ten papers contained two major contributions to the understanding of obstetric injuries to the nervous system of the fetus: "Changes of Pressure Inside the Fetal Craniovertebral Cavity"[1] in 1923 and "Obstetrical Injuries of the Spinal Cord"[2] in 1927 with Dr. Marian Putnam. These have profoundly modified obstetrical procedures and the understanding of neurological deficits. Of the first he often told me that he had peddled the manuscript from editor to editor for six months, until a note from Dr. Harvey Cushing brought about its publication.

With the sympathetic backing of Dr. Kenneth Blackfan, the Thomas Morgan Rotch Professor of Pediatrics at Harvard, Dr. Crothers set about implementing his plan for a neurological department at the Children's Hospital. A tour of the medical centers of Europe and financial support from many quarters resulted in construction of a ward floor and an office floor for the department in the Hospital. His original concept was, I think, of a more or less isolated portion of the Hospital to which children with fixed lesions of the nervous system might be admitted for teaching, training, or control of seizures. Experience of a year or two was adequate to convince him that the basic motor and intellectual functions of the nervous system were little modified in small children by teaching of various sorts, and that the setting of functional goals at levels beyond ready achievement was fraught with important emotional peril for patients.

Improved diagnostic appraisal became his next goal. With Dr. Elizabeth Lord, whom he had attracted from Dr. Arnold Gesell's Institute of Human Relations in New Haven, he set about this task from the psychologic point of view. With her clarification of psychologic techniques it soon became apparent that global psychologic scores, for example the I.Q., failed to define the assets and liabilities of individuals suffering from cerebral injury but that useful descriptions could be formulated. With Drs. Wyatt and Vogt, he explored the diagnostic usefulness of pneumoencephalography in the definition of cerebral disease states, concluding in the long run that, while the method was useful in helping to define fixed as opposed to certain progressive lesions, there was no close relationship between the deficit of brain mass, so demonstrated, and cerebral function. During his European tour he had become interested in the work of Magnus on "postural motility" and had suggested to me its possible importance in the diagnostic assessment of cerebral palsy. With his encouragement a good deal of translating was done, and cases followed over a period of years, resulting in a report on tonic neck reflexes which he insisted should be published under my name, "since," as he said, "anyone who has translated all that German should certainly get the credit."

Much as he enjoyed and participated in all that was going on around him, he became increasingly aware of the importance of personality formation in children, especially in those with handicaps. The Mental Hygiene Movement seemed to him both important and perhaps poorly directed, and in 1937 he published a volume entitled *A Pediatrician in Search of Mental Hygiene*.[3] The volume needs to be read as a whole to be understood, but perhaps a few quotations

from the introduction and conclusions will define its aims and scope. In his introduction he discusses the relationship of doctors to mental hygiene and states (page viii), "The doctors have rested, pretty complacently, on the theory that, if mental hygiene is good, people will come to them for it, and that they will, by intuitive wisdom and common sense, be able to answer all questions, or at least silence the questioner. Unfortunately, this attitude has had, in the past, some basis in fact. Even as things are now, the doctor, by ruthless use of medical prestige, can block inquiry about mental and emotional problems to a considerable extent. This power is presumably transient. 'Mothers' and 'children' come along in continuous series and pass through and beyond the period of pediatric supervision. The pediatrician who is standing on the general platform that the doctor, as the heir of all medical wisdom accumulated since Hippocrates and Galen, need fear no rival, is taking chances of considerable and perhaps uncomfortable disillusionment. On the other hand, he is in a position of considerable natural strength if he chooses to include in his concept of pediatrics an intelligent interest in the confused but fascinating problems covered by the general term of mental hygiene."

And later in his introduction (page xvii), "In this discussion I am trying to find a way of changing the conditions under which pediatricians are trained, so that they may gain acquaintance with the behavior of children without interfering with what I believe is the more essential duty of teaching pediatricians the care of physical disease. In saying this, I am making an assumption which may be incorrect, but I believe that promptness, accuracy and competence in the physical care of children is obligatory in pediatrics. Any plan which does not recognize this as a starting point is unacceptable to most doctors and parents."

In conclusion, he discusses suggestions of his own and of others as to how the dilemma presented by competence in physical disease as opposed to competence in relation to personality development might be resolved, and after due reference to others, states (page 269):

"One suggestion which has been made a great many times is that the pediatrician is already competent, by the nature of his practice, in the field of mental hygiene. I have looked for such men many times, so far I have not found very many. Another suggestion is that pediatricians, as they stand, are doing all they can, and need not bother with any attempt to make further studies of mental hygiene. This seems to me absurd since every pediatrician gives advice about habits, schools, and so on. He may be practicing good or very bad mental hygiene, but, unless he is one of a few specialized consultants in restricted fields of medical practice, he always practices something of the sort.

"It is a tempting but rather futile solution to surround a willing pediatrician with a crew of subordinates from various fields who will do his bidding. A smoothly running machine can unquestionably be constructed, but such a method will not teach the pediatrician or his students very much.

"A less predictable scheme, which it seems to me holds more promise, involves the pediatrician in interesting trouble. If he selects a group of competent people to help him formulate terms on which pediatricians can participate in mental hygiene, he must offer to listen to criticisms of management, to consider whether limitations or even transfer of medical authority, in specific situations are wise, to discuss the validity of nonmedical ideas on medical matters and so on. Clearly profitable controversy of this sort cannot be conducted on general wards, but only with carefully selected people, in a segregated but not inaccessible part of a teaching hospital, can it be carried out without difficulty.

"It seems evident that previous methods have not led to effective participation in mental hygiene by pediatricians. A carefully considered attempt to discover the pediatric field seems worth trying. It may well be that the field will be limited. It seems en-

tirely clear that it will not be identical with those suggested by the propagandists, but will be surveyed by people who are thoroughly aware of the value of the pediatrician as he exists, and it will not involve those who enter it, in commitments which prevent them from meeting their fundamental duty of giving prompt, effective and intelligent care to sick children."

Written before the days of wonder drugs of all sorts, these notions are as important today as then. If these quotations have stimulated a few to read this nearly unobtainable book, they will have been worth while.

At about the time of his retirement he became acquainted with two visitors from England both of whom influenced him, and he them. One was Dr. Honor Smith who came to this country because of her interest in tuberculous meningitis and who stayed to write a paper with him on the hazards of pneumoencephalography.

In 1952 he retired and undertook the follow-up study of cerebral palsy. Dr. Peter Tizard joined him in the first few months of this work, publishing observations of hemiplegia. Dr. Crother's influence on Dr. Tizard is well exemplified in the paper presented by him and others at the International Congress of Pediatrics in Montreal in 1959 on "The Role of the Paediatrician in Mental Illness,"[4] a paper in which the authors have offered a most grateful recognition of Dr. Crother's contribution to the field.

His interest in cerebral palsy was sustained throughout his professional life and culminated in the posthumous publication of *The Natural History of Cerebral Palsy*,[5] in co-authorship with Dr. R. S. Paine. This work, perhaps better than any readily available, sets forth his paramount concern with the personality of his patient as opposed to an interest in details such as articulation, gait, or posture. The conflict between what he knew was expected of him and what he felt he could honestly say about the evolution of cerebral palsy is apparent throughout the book. The introductory paragraph to the chapter on "The Intelligence of Individuals With Cerebral Palsy" is characteristic: "We now approach the complicated task of putting our results [with regard to intelligence] into definite form. We recognize that some generalizations are essential and we dutifully present a few charts, but we precede and accompany them by emphatic reservations." Again, as in the book on mental hygiene, he recognized and tried to depict the complicated variability of nonselective cerebral disease in infancy, and to point out that even in the face of such injuries, growth and development of some degree were certain to occur. Since, however, growth and development were modified downward, the period of dependence on parents became unnaturally prolonged.

The book is important as a longitudinal study of individuals with fixed cerebral lesions, and as such is probably unique. The patients were selected because they presented motor defects, but the importance of accompanying cerebral functional disabilities is thoroughly described. These include, intellectual, epileptic, cerebral sensory, and emotional disturbances, and finally the sociologic effects of the disease on the patient and his family. The chapter on "Emotional Status in Adolescence and Adult Life," though admittedly an anecdotal presentation of cases, revealed Dr. Crothers at his perceptive and sympathetic best. It points out the great importance to the patient of the attitude of his family. This seems more important than the exact type of lesion (as long as it is not too severe) or the exact degree of mental deficit (with the same reservation). The sine qua non for those who succeeded in life in spite of their cerebral palsy appears to have been a family constellation exhibiting confidence in and warm affection for the patient and acceptance of his experimental strivings for independence. Efforts to orient the family in this regard seemed to Dr. Crothers among the most important therapeutic measures to be taken.

At least fifty-six papers or books were published by him, and all dealt with various aspects of the subjects upon which we have touched, save for one small volume on *Neu-*

rology in Childhood. How many other publications by associates were inspired by him is impossible to estimate, but there must be many. Dr. Edith Meyer Taylor, associated with him during the last years of his active work at the Children's Hospital, has, for example, published a valuable volume on the *Psychological Appraisal of Children With Cerebral Defects,*[6] the outcome of experience in working with many groups, but particularly with Dr. Crothers in Boston.

As a teacher he had a most important impact on house staff and students—disarmingly straightforward and seldom didactic. Often he took a patient and mother, both strange to him, before a class and made of the occasion not only an interesting teaching exercise for the students, but also a rewarding interview for the parent. He was always careful to protect the self-respect of all, and his adroitness in interview brought point after point to the attention of student and parent, allowing both to draw their own conclusions. Always alert to the functional significance of any occurrence, he had the faculty of quickly discerning the heart of the matter at hand, and stating it succinctly, once his listeners had been guided to the same, though perhaps less clearly perceived, conclusion.

In a long association, I never knew him to take anything but the most generous stand in support of his associates. He insisted on rigid search for and adherence to facts, but once these were ascertained their statement in scientific literature could not be modified. One of my most vivid recollections is of a visit by a representative of industry who appeared bent on instituting trouble over the suggestion of Dr. Elizabeth Lord and myself that lead might damage the nervous system of young children. Bronson took us all to a lunch, which ended by the representative of industry offering to bear some of the expense of further inquiry into the matter. A firm friendship, which has persisted to the present, was started through his forceful yet friendly discussion, sticking conscientiously to facts, but lubricated by judiciously dispensed food and drink. Though he was a rugged person, uncomfortable when giving or receiving praise, nevertheless, he gave his support painstakingly and generously in time of need.

The American Pediatric Society honored him with its presidency in 1951, to his intense gratification. The older members will recall his presidential address, from which the two slides (Fig. 2) were taken. It made the prediction that cerebral palsy would have to come to be considered in terms of modification of adult life, rather than childhood

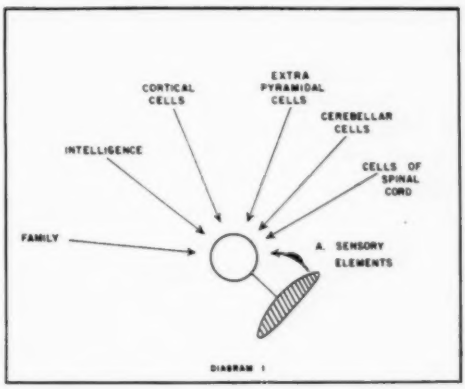

Fig. 2. Diagram 1, The many factors influencing the activity of children. Diagram 2, Attainment of independence. (From Crothers and Paine: The Natural History of Cerebral Palsy, Cambridge, 1959, Harvard University Press.)

protection. His ever-ready sense of humor was well brought out at the meetings by his admonition, "Some of the discussers, whether through modesty or arrogance, are failing to give their names on arising." Thereafter, identification was prompt and complete.

He was also President of the Boston Society of Neurology and Psychiatry in 1940, and of the Academy of Cerebral Palsy in 1951. In May of 1959 he was intensely gratified to be notified of his selection for the Howland Award by the Society. In failing health from spinal muscular atrophy for the last two years of his life, he died suddenly on July 19, 1959, soon after his seventy-fifth birthday.

Characteristically, he ended his book on mental hygiene, which he thought of as being unconventional and critical of doctors, with the sentence, "There is a certain inconspicuousness about being under a cloud that is rather restful."[3] Medicine did not permit him to hide under his cloud, and he did enjoy life to the full. Such enjoyment in a person of his discernment could have been achieved only with the loving support of his wife, who is with us today.

RANDOLPH K. BYERS, M.D.

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Books

Modern Problems in Pediatrics—VI.

A. Hottinger and H. Berger, Editors, Basel and New York, 1960, S. Karger, AG., 560 pages. Price $23.50.

The sixth volume of this publication deals entirely with renal function and kidney disorders in childhood. To the reviewer's knowledge this is the first attempt at presenting present-day knowledge in this field under one cover. Even granting the large gaps in our knowledge and the occasional poorly organized presentation, the goals of this book are to be admired.

Twenty-seven chapters are presented by an array of distinguished authors, each of whom is a recognized authority. A number of grammatical and typographical errors are glaringly evident and may be due to the trilingual character of the book. Eight chapters are in English, 6 in French, and 13 in German. While certainly something would be lost in translation, is it not expecting too much of the physician for him to be facile in three languages? My objections do not involve criticism of the subject matter (which is excellent and sorely needed) but are mainly directed at the multilingual method which resulted in a sense of pique caused by inability to read several chapters with fascinating titles.

DANIEL S. FLEISHER, M.D.

Studies on the Technique of Skin Testing in Allergy. W. J. F. van der Bijl, Springfield, Ill., 1960, Charles C Thomas, Publisher, 100 pages. Price $5.00.

This little volume, originally published as a thesis, presents the commendable effort of the author to systematize the variables surrounding skin testing in the study of allergic disorders. The observations reported, while of interest, add nothing exceptionally noteworthy to present information and lack sufficient statistical depth either to permit resolution of current differences of opinion (in such areas, for example, as effects of drugs on reactivity of skin) or to indicate with confidence what testing techniques can be considered as standardized.

VICTOR C. VAUGHAN, III, M.D.

Intraspinal Tumors of Childhood.

Robert W. Rand, M.D., and Carl W. Rand, M.D., Springfield, Ill., 1960, Charles C Thomas, Publisher, 544 pages. Price $16.50.

This book has been written expressly for the neurosurgeon but it can also be a valuable reference text for the pediatrician.

The authors have described in detail the numerous neoplastic diseases as well as the expanding nonneoplastic lesions that involve the spinal canal and the contained neural structures.

Emphasis is placed on the diagnosis of these infrequent lesions. As with intracranial tumors in childhood, the diagnosis is often delayed because of the readiness to attribute nonspecific symptoms, such as backache, abnormal gait, chest and abdominal pain, or even weakness of an extremity, to diseases other than neoplasm. Of special interest to the pediatrician in this respect is chapter 21 which deals with the general considerations and diagnosis and management of intraspinal lesions in childhood.

The book is profusely illustrated with 72 case histories, among which the reader may find the answer to that puzzling case in his practice which has been defying diagnosis.

FREDERICK MURTAGH, M.D.

News and notes

The Sub-Board of Pediatric Cardiology of the American Board of Pediatrics announces that its organization is complete and that it is now ready to accept applications for certification both on record and by examination. The former must be submitted by Dec. 31, 1961.

Applications for approval of residency training programs in pediatric cardiology will also be accepted.

Full information and application forms may be obtained from The Executive Secretary, American Board of Pediatrics, 6 Cushman Road, Rosemont, Pa.

The members of the Sub-Board of Pediatric Cardiology are: James W. DuShane, Chairman, Rochester, Minn.; Forrest H. Adams, Los Angeles, Calif.; Edward C. Lambert, Buffalo, N. Y.; Alexander S. Nadas, Boston, Mass.; Saul J. Robinson, San Francisco, Calif.; and Helen B. Taussig, Baltimore, Md.

The Bronx Pediatric Society will hold its monthly meeting on April 12, 1961, at 8:30 P.M., in the Morrisania City Hospital Auditorium, 168th St. and Walton Ave. Dr. Robert Goetz and Dr. Richard Friedenberg, both of Albert Einstein College of Medicine, will speak on "Diagnosis and Treatment of Left to Right Shunt."

A **continuation course in pediatrics** for general practitioners and specialists is being presented at the **Center for Continuation Study,** University of Minnesota, Feb. 27 to March 1, 1961. Visiting faculty includes Dr. Edward A. Mortimer, Jr., of Western Reserve; Irving Schulman, of Children's Memorial Hospital, Chicago; and Robert J. Slater, of the University of Toronto and Sloan-Kettering Institute for Cancer Research. Members of the faculty of the University of Minnesota Medical School and the Mayo Foundation will also participate. Lodging and meal accomodations are available.

The Tenth Annual Post-Graduate Seminar for Pediatricians will be presented at St. Christopher's Hospital for Children by the Pediatric Department of Temple University's School of Medicine in Philadelphia, May 24 to 27, 1961. Principal emphasis will be on recent developments in pediatric endocrinology and metabolic disturbances.

For information regarding enrollment, registration, fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pa.

A **fellowship** in the **Children's Epilepsy Clinic** of the Johns Hopkins Hospital will be available on July 1, 1961. Patients of all ages and with all types of seizures are received in this clinic. The fellowship offers an opportunity for training in diagnosis and management of patients with seizures and in the practical aspects of electroencephalography, as well as for participation in clinical investigative projects. The stipend will be discussed with the candidate. Any physician interested should communicate with Dr. Samuel Livingston, Harriet Lane Home, The Johns Hopkins Hospital, Baltimore 5, Md.

The Department of Pediatrics of the University of Utah College of Medicine, under a training grant from the National Institutes of Health, offers a **fellowship in endocrinology and metabolism.** An opening will exist as of July 1, 1961; other initiation dates may be arranged. This program offers opportunity for investigation and training in the fields of endocrinology, metabolism, and genetics. It is desired that applicants have completed at least one year of residency training; in special instances other training may be considered. Inquiries should be addressed to Esten W. Ray, M.D., Department of Pediatrics, University of Utah College of Medicine, Salt Lake City, Utah.

Two traineeships in pediatric endocrinology, metabolism and renal disease will be available at the Los Angeles Childrens Hospital as of July 1, 1961, for applicants with at least 2 years' residency in pediatrics. The traineeships, designed to lead to careers in academic medicine and research, will ordinarily be for 2 years, although applicants for 1 year will be considered, and extension of training for more than 2 years is also possible. Address correspondence to Dr. S. A. Kaplan, Childrens Hospital of Los Angeles, 4614 Sunset Boulevard, Los Angeles 27, Calif.

Traineeships are being offered at Philadelphia General Hospital in **Experimental Nutritional Science.** Trainees are to be selected from applicants with a doctorate in medicine or related fields; they will work for 1 or 2 years under Dr. Paul Gyorgy, of the Department of Pediatrics, and will have the opportunity of obtaining advanced degrees. Inquiries should be addressed to him, at Philadelphia General Hospital, 34th and Curie Avenue, Philadelphia, Pa.

EDITOR'S COLUMN

Susceptibility to rheumatic disease

A RECENT report on "Acute Rheumatism and Paediatric Beds"[1] calls attention to "the possible recrudescence of diseases thought to be in decline" and observes that "although we may have been able to reduce the relapse rate [of rheumatic fever] by regular prophylactic penicillin, prevention of the first attack has not been achieved." One may reasonably anticipate that cyclical fluctuations in the incidence and severity of rheumatic fever are to be expected in the future. Moreover, the fundamental problem —why only a small percentage of humankind is susceptible to rheumatic fever—has barely been recognized.

In contrast, many encouraging advances are being made in investigating the factor of infection in the rheumatic state. Furthermore, immunologic studies on allied collagen diseases are developing new indications that the mechanism of autoimmunity may also be significant in the pathogenesis of rheumatism. Irrespective of the mechanics and the antigenic determinants involved, even if the rheumatic state should prove to be a secondary antigen-antibody reaction, there remains the most important, most challenging, but most neglected fact in the genesis of rheumatic fever, namely: Under the most "favorable" environmental conditions, only about 5 per cent of human subjects are susceptible, are reactive to the antigenic determinant. What critical factor controls this peculiar reactivity of the small minority?

More than half a century ago, this matter of the host factor of Cheadle's[2] rheumatic state engaged the interest of British clinicians. One of these, Sir Archibald Garrod,[3] envisaged certain disease syndromes as inborn errors of metabolism and described four rare metabolic disorders. Even in this early period of enzymology Garrod postulated that certain diseases represented deficiencies in enzymes essential for handling normal metabolites. Progress in methodology has widened the scope of Garrod's concept and demonstrated that genetic variation may be followed by the synthesis of certain proteins which vary only slightly from the normal chemically but vary greatly in their biologic activity. Garrod's original four diseases were apparent at birth or shortly thereafter, but it has become clear that other inborn errors of metabolism may not manifest themselves for many years. Diabetes mellitus is now a well-recognized example, and I believe that rheumatic fever may prove to be the "opposite side of the coin." In connection with slowly developing metabolic disturbances, the work of Williams and co-workers[6] indicates that in many diseases of obscure etiology there may be present "geneotrophic factors—those in which the genetic background and nutritional factors jointly enter into the etiology." It is the role of this combination (inborn error aggravated by inappropriate diet) which now warrants the attention of those concerned with the mechanism of rheumatic fever.

That nutrition is a significant factor of

environment, few will deny. The concept that diet in early life may modify susceptibility to disease states is still nebulous and has relatively few adherents. It is known, however, that choline privation for only a few days in the early life of the rat induces kidney lesions with subsequent fatal cardiovascular-renal disease in adult life.[5, 6] Peete[7] and more recently Johnston[8] have called attention to the possibility that faulty nutrition may play a significant role in the genesis of rheumatic fever. Moreover, in studying recurrence rates in rheumatic children, given special dietary attention and no prophylactic agents, Jackson[9] concluded: "The most significant association between the environmental factors and the distribution of recurrences was found for the dietary factor."

What is this hypothetical nutritional protective factor? If its lack be a characteristic of low-income diets, this may explain the "clear-cut social incidence" emphasized by many investigators, especially by Glover.[10] Is there any significance to the observations of a relation between a low intake of a foodstuff and rheumatic disease? Wallis[11] found that in patients with rheumatic heart disease there was a history of low egg consumption and/or a low level of serum phospholipids in 80 to 90 per cent of persons studied. It is common experience that declining susceptibility to rheumatic fever parallels improved standard of living, including better nutrition. In areas where there evolve more liberal diets for infants and in families which suddenly experience substantial increases in income and buy more of the expensive foods, rheumatic fever morbidity rates fall strikingly to a small fraction of prior levels.

In America, infant feeding has become progressively more liberal and varied since the turn of the century. Furthermore, families have been urged by nutritionists to give their school children several important foodstuffs (including large quantities of milk, as well as poultry, meats, and eggs). Nevertheless, the basis for this evolution in child feeding remains largely empirical. For example, if there be any requirement for egg by humankind, and in particular by the rheumatic subject, it is unknown. And yet, there are some suggestions that the needs of the rheumatic subject may perhaps differ from those of his siblings. Studies of Chang[12] in Chicago and Appleton[13] in New York indicate that subjects with quiescent rheumatism have relatively low blood lipid levels. If these observations of differences between rheumatic subjects and their nonrheumatic siblings be correct, one may reasonably speculate that there is an inborn error in the metabolism of lipids. Then rheumatic fever will prove to be a disease in which the genetic background and nutritional factors jointly enter into the etiology.

The demonstration or elimination of this possibility will, of necessity, be confounded by the fact that rheumatic fever is a summation disease, requiring not only a genetic diathesis, but also a *conditioned host*, as well as a particular precipitating bacterial agent. Whereas it is now generally accepted that infection with Group A hemolytic streptococcus is an essential component, it is not well recognized that some unidentified product of the streptococcal strain is required to activate the rheumatic process. The capacity to produce this "rheumatogenic substance" appears to vary from strain to strain. Some outbreaks of streptococcal throat infections among rheumatic children induce no detectable rheumatic activity, whereas similar outbreaks caused by a different streptococcal strain (even of the same serologic type) may induce among the same children rheumatic attacks of great intensity. This "rheumatogenic substance" has not been defined and remains a variable that cannot yet be evaluated.

The current decline in clinical attacks of rheumatic fever in persons with untreated streptococcal infections may indicate either decreased susceptibility of the host, decreased incidence of streptococcal infection, or decreased "rheumatogenicity" of the prevalent strains. When the last occurs it is probably only a temporary cyclical fluctuation. This was pointed out in a recent re-

port from New York City where the mildness of rheumatic fever for some years had suggested that highly "rheumatogenic" strains no longer existed. However, in 1959, 2 Puerto Rican children were observed with the most florid rheumatic manifestations.[14] A girl with a first attack died on the initial day of cardiac symptoms with fulminating pancarditis, accompanied by extensive and intense coronary arteritis. A boy, also in a first attack, survived severe and prolonged polycyclic disease with five crops of rheumatic nodules. Not only did this lad reproduce the full distribution of subcutaneous nodes shown by Cheadle[2] in the frontispiece of his monograph, but he even had these lesions on his elbows, fingers, and knees. In these 2 children living in poverty, streptococcal strains appeared highly rheumatogenic. If provided with properly conditioned hosts, prevalent hemolytic streptococci can still induce rheumatic fever with as great intensity as ever recorded. The warning by Smallpiece and Ellis[1] is as significant in New York as in Oxford. Important as ever is the need for a method to prevent the maturation of the rheumatic state. The most encouraging approach to meeting this challenge among low socioeconomic groups may well be the improvement of diets during early childhood.

Circumstantial evidence has been presented that one factor in the improved nutrition of young children may be increased consumption of egg yolk.[15] Experimental evidence has shown that at least one fraction found in the alcohol-soluble material of egg yolk has antiallergic activity of high potency.[16, 17] Recently this compound, N(2-hydroxyethyl)-palmitamide, $CH_3(CH_2)_{14}$-$CONH(CH_2)_2OH$, prepared by scientists of Merck and Company,[18, 19] was fed to New York City children of rheumatic fever families.[20] Altogether 95 suitable families (mostly Puerto Rican) volunteered to enter this study to determine whether this compound would modify susceptibility to rheumatic recurrences, and they provided over a 2 year period 95 rheumatic school children and 152 siblings below the age of 15. Concomitant dietary information was obtained at three points during this investigation.

This double blind study indicated that the egg yolk compound tested in amounts as large as 75 mg. daily had no untoward effects. At the end of 2 years, statistical evaluation of the potential effectiveness of the compound was not accomplished, because of the rarity of rheumatic recurrences during the period of this investigation. Even though the incidence of proved hemolytic streptococcal throat infections was high in the families studied, only 7 rheumatic recurrences occurred in patients among whom 25 to 40 had been anticipated in a period of 2 years. Of these, 6 occurred in the placebo (control) group. The other patient, who developed rheumatic activity during the fifth week of palmitamide prophylaxis, had received less than 2 Gm. of the compound when he contracted streptococcal infection.

An uncontrollable variable in this study was the general improvement in diets that occurred. Even though low-income families continued to receive Welfare funds and to live in New York's poorest, overcrowded, slum tenements, their diets improved markedly over what they had been in Puerto Rico. The marked increase in egg consumption to a mean exceeding 7 per week by rheumaic children "contaminated" this investigation on the possible usefulness of an egg yolk component. If this or other food fractions are to be tested on rheumatic children in the future, one must find a population in which the standard of living, the family diets (including infant feeding), and the egg consumption can reasonably be expected to continue at a minimal level throughout a period of several years.

It remains to be determined whether: (a) the rheumatic subject may have a metabolic peculiarity, for example in lipid metabolism; (b) susceptibility to the rheumatic state may depend in part on nutrition in early life; (c) the consumption of sufficient egg yolk, or a fraction thereof, or a combination of food factors may afford protection against rheumatic recurrences and first attacks. Of

key importance is the defining and clarification of rheumatic susceptibility. The key question in the pathogenesis of rheumatic fever is: Why is only a small percentage of humankind capable of entering the rheumatic state?

ALVIN F. COBURN, M.D.

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Thoughts about pediatrics

PUBLISHED discussions and correspondence plus personal conversations with colleagues suggest that we do not all define Pediatrics in the same way. I shall start with a definition because what follows will then be more meaningful.

Pediatrics is that branch of medicine which deals with the problems of health and disease as influenced by the factors involved in growth and development.* It is these factors that differentiate the child from the adult and form the basic structure for pediatrics as a medical specialty.

Great advances have been made in knowledge of the child and his unique characteristics since the realization of a few wise

**These terms, wherever they appear, are intended to convey their broadest meaning: anatomic, physiologic, intellectual, emotional, social.*

physicians nearly a century ago that the child was not just a miniature man; with the knowledge available the earmark of good pediatric care for more than fifty years has been "comprehensive care and guidance" and "treating the child as a whole." We do not have a "new pediatrics," we have a better pediatrics because of a greatly increased body of knowledge. We should, however, seriously ask whether the reason for dissatisfaction expressed by some pediatricians may not be because they are not actually practicing pediatrics as a specialty. It is my belief that, omitting those unsuited by personality, temperament, and motivation, this is the chief cause. If this is true, inadequacies in pediatric education and in training for the practice of pediatrics are largely to blame and should be corrected.

With the rapid accumulation of new scientific medical knowledge there has been a tendency, in the training of pediatricians, to neglect the basic concepts upon which the specialty rests. Much could be done to remedy this through full and proper use of available facilities and by conscious effort to emphasize whenever possible the special features that are characteristic of the child. It is the intimate and thorough understanding of the child that gives the pediatrician his status as a specialist.

We have facilities well suited to this kind of training: outpatient departments, newborn nurseries, child health conferences, units for care of adolescents in some centers, and the inpatient service when properly used. All are excellent for such training, and full advantage should be taken of them in proportion commensurate with their importance to the practice of pediatrics as a specialty. Good supervision by physicians with knowledge and experience is essential for good training. Proper diagnostic and therapeutic methods and doctor-patient relationships are best taught by supervision and example. It makes "learning by doing" when in practice more comfortable and meaningful. Example and demonstration while in training can make the pediatrician more adept in handling children and in counseling parents and add much to his success and pleasure in practice.

The unique doctor-patient relationship, the most precious heritage of physicians from their predecessors, should, and I hope can, be preserved. I believe pediatrics is in a strategic position to do more for its preservation than any other branch of medicine. The widespread criticism of doctors today results almost entirely from failure in human relations, not from lack of scientific knowledge and technical skill. Pediatric training could do much more than it has done to emphasize this aspect of the physician's role.

We need now to consider seriously whether or not this sort of essential training can still be adequately given without extending the two-year period of training now required for Board certification to three. We know it can and has been done satisfactorily for the majority of trainees in the past, but the increasing number expressing dissatisfaction indicates the need of some serious stocktaking and re-evaluation, before we conclude that this two-year period will continue to be adequate. There are two major considerations: (1) how best to serve the health needs of the nation's children, and (2) how best to preserve and strengthen the status of pediatrics as a specialty. Both of these have, I know, been subjected to the thoughtful and penetrating judgment of many pediatricians, academicians, practitioners, and Board members, and there is still honest difference of opinion. The arguments presented by Drs. Lee Hill and John Mitchell for continuation of the present required two-year program published in the August, 1960, issue of this JOURNAL must be taken seriously because these men, through long and continuous service on the Board, speak from intimate knowledge of existing conditions. The arguments of Dr. Waldo Nelson in that same issue favoring a three-year training period, though not yet as a requisite for Board certification, coming from a pediatric educator, should receive equally serious attention as an indication of a definite trend of serious thinking.

Dr. Hill and Dr. Mitchell both speak of the great improvement in the medical care of the nation's children within the last thirty years; they imply, by quoting figures showing the great increase in the number of practicing pediatricians, that the improvement is due to this increase, and Dr. Mitchell states that "any action on our part to delay or reduce the number of physicians entering the practice of pediatrics in the years just ahead would, in my mind, be a serious disservice to the children of the country." There is a confusion of terms here—pediatrics and pediatrician are not synonymous. The influence of pediatrics has been a tremendous factor in improving the medical care of children but let us not be so immodest as to claim undue credit for the increased number of practicing pediatricians, and certainly not for those who have an assembly-line type of practice. I have witnessed the great and continuous improvement in the care of children by general practitioners in my professional lifetime and, like quite a few others, remember clearly the efforts necessary to convince a medical faculty that a separate department of pediatrics should be established. It is not realistic to expect that much more than half of the nation's children will ever be cared for by pediatricians, so I am not selling the general practitioner short in spite of his obvious need for more pediatric training. I cannot agree, therefore, that reducing the numbers of physicians entering pediatric practice would be a serious disservice to the children of the country. I would add also that while pediatrics can well be proud of its role in improving the health of the nation's children, a large part of this improvement has followed naturally that of the health of the public as a whole, as a result of a multitude of factors that have made for better living conditions. Indirectly, this too has been, to a significant degree, due to advances in general scientific medical knowledge.

Our efforts to fulfill our responsibility to the health of the nation's children will continue and, I believe, will in the long run be more adequately met as we improve the pediatric education of all medical students as well as those who choose to practice pediatrics, even if their number is smaller. So I do not think the health of our children will suffer. But I am seriously concerned about the specialty status of the pediatrician in practice.

No one can say precisely how long a period of training is necessary today to equip a man for the practice of pediatrics as a specialty. There is good evidence that two years has been adequate for the majority of trainees in the past and it almost certainly could be an adequate period today with a training program properly formulated and conducted. In my opinion it is no longer merely a question of whether the required residency period for certification should be two years or three, but rather one of either, or; *either* the two year program must be properly formulated and conducted to prepare the trainee for the practice of pediatrics as a specialty; *or* a third year will need to be added to accomplish this. I believe, however, that with the rapid advances in medical knowledge it will prove increasingly difficult from now on to do the job well in two years and that much better training will result from an additional year of residency.

The third-year resident could most profitably spend a major portion of his time obtaining a more thorough and intimate knowledge of the child and his characteristics at the various stages of his growth and development, and learn about parents, their concerns, and how to answer their questions and give counsel to them. With the improved health conditions and the great reduction in the incidence of serious communicable and nutritional diseases, it is essential that all physicians, and particularly pediatricans, become increasingly health minded and less exclusively disease minded. The pediatrician needs to know more about the well child, about his home, school, and community environment. Facilities for this sort of training are to be found in practically all institutions approved for pediatric

residency training: newborn nurseries, outpatient departments, well child conferences, child development clinics, child guidance clinics, and the like. This is essential knowledge for pediatric practice; it is the knowledge he will have greatest need for. In obtaining this knowledge he should be given a large amount of personal responsibility, but he will also need instruction. He may at first see little of interest in well newborn infants, or babies, or children, or adolescents, unless their fascinating and unique characteristic features and reactions are pointed out and demonstrated by an experienced teacher. And here is where an experienced practicing pediatrician could be most effective as a teacher.

The trainee could, if he desires, spend part of his time in a pediatric subspecialty, but this does not seem to me to be the best use of his time; it could more profitably be spent in the pathology and x-ray departments as far as training for pediatric practice is concerned. Proficiency in a subspecialty requires time and is not truly a function of pediatric training for Board Certification; it should be the physician's own responsibility to obtain it later if he desires.

Consultations have a heart-warming effect but are not necessarily the badge of a specialist. The man who does a superior job will not only have plenty of patients but also some consultations, and nearly all of them indirectly through recommendation of satisfied patients and only a small proportion directly from other physicians.

In conclusion, I believe that the time has come, or is close at hand, for the addition of a third year to the requirements for Board Certification in order to prepare physicians properly for the practice of pediatrics as a specialty and protect the specialty status of all practicing pediatricians. It would serve to eliminate those ill suited for pediatric practice and would lessen the number of dissatisfied pediatricians. While conscious of the fact that there would be a sharp decrease in the number who choose pediatrics as a specialty, I am not as concerned as Dr. Hill and Dr. Mitchell have said they are. The advantages seem to me to be greater than the disadvantages and I have a strong feeling that in the long run the nation's children will be better served by a smaller number of pediatricians with better training who will practice pediatrics like specialists, feel like specialists, and have the status of specialists in the community.

The strongest objection raised by Dr. Hill and Dr. Mitchell is the insufficient number of training centers suitable for three years of residency training. I cannot answer this objection adequately. It would be valid, of course, if the number of trainees should remain at the present level, but it might not be for the smaller number that will result from the changed requirements, and this objection certainly would be surmountable if the third year were not devoted to subspecialty training, as some propose, but to the use of outpatient facilities, pathology, and x-ray, as I have suggested.

ARTHUR HAWLEY PARMELEE, SR., M.D.